REVIEW ARTICLE

The spectrum of thyroid diseases in childhood and its evolution during transition to adulthood: Natural history, diagnosis, differential diagnosis and management

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ABSTRACT. In this contribution, we review current knowledge on the pathogenesis, diagnosis and differential diagnosis of thyroid disorders in childhood and adolescence, as well as present an update on therapy methods and management guidelines for these disorders. This overview is conceptually divided into two parts, one focusing on thyroid functional disorders, *i.e.* conditions leading to hyper- and hypothyroidism, and another one pertinent to structural abnormalities of the thyroid gland, *i.e.* nodular disorders and thyroid cancer. Currently, congenital hypothyroidism is diagnosed in a much more timely fashion rather than in the past, rendering hypothyroidism-related mental retardation and developmental deficits very rare in newborns and children and, hence, diminishing significantly its public health impact. At the same time, considerable advances have occurred in our understanding of the molecular basis of several genetic conditions affecting the thyroid gland in childhood, such as familial non-autoimmune hyperthyroidism, as well as of the pathways leading to thyroid neoplasia.

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INTRODUCTION

Here, we review common and less common thyroid disorders in children and adolescents by subdividing them into functional and structural categories. We will not discuss inherited syndromes that are characterized by changes in the structure or amount of thyroid hormone (TH)-binding serum proteins, resulting in problems with TH measurement and misinterpretation of thyroid function testing. We also will not elaborate on inherited and acquired conditions that may result in pathologic changes in the process of T_4 deiodination, as is the case with the euthyroid sick syndrome.

Key-words: Adolescence, childhood, congenital, goiter, hyperthyroidism, hypothyroidism, infancy, iodine deficiency, levothyroxine, radioactive iodine, thyroid cancer, thyroid gland, thyroid hormone, thyroid nodule, thyrotoxicosis, thyrotropin.

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The physiologic function and growth of the thyroid gland is based on the normal association among the different regulatory elements of the hypothalamo-pituitary-thyroid (HPT) axis. Higher brain centers project upon specific hypothalamic areas, which in turn are responsible for the neurosecretion of TRH in the *zona externa* of the median eminence. TRH then reaches the pituitary thyrotroph cells and controls synthesis and secretion of TSH, which, in turn, stimulates secretion of TH by the thyroid gland, as well as glandular growth (1). The main hormone secreted by the thyroid gland is T_4, although small amounts of T_3 are also secreted. In both the hypothalamus and the pituitary gland, T_4 is converted to T_3, which eventually acts to inhibit further pituitary release of TSH. Circulating TH in plasma are bound to TBG, TBPA and albumin, with only the unbound (free) fraction of the hormones being metabolically active. Serum T_4 stems exclusively from the thyroid gland, whereas 80% of serum T_3 is derived from peripheral (mainly hepatic and renal) 5'-mono-deiodination of the T_4 molecule (2). Eventually, T_3 enters its target cells and gains access to the nucleus, where it is bound to highly specific receptor

proteins, *i.e.* the TH receptors (TR). These are ligand-regulatable transcription factors, which bind directly to DNA, leading to transcriptional regulation (activation or silencing) of specific genes (3).

FUNCTIONAL DISORDERS OF THE THYROID GLAND IN CHILDHOOD AND ADOLESCENCE

Hyperthyroidism

Hyperfunction of the thyroid gland, or thyrotoxicosis, is less common in children than hypothyroidism. In the neonatal period, Graves' disease is rare and occurs in about 1 out of 70 cases of thyrotoxic pregnancies (4, 5). Less than 5% of all cases of Graves' disease present clinically during childhood, with recent studies reporting an incidence of 10^{-7}/year (6, 7).

Transplacental passage of TSAb from mothers with Graves' disease causes neonatal autoimmune-mediated thyrotoxicosis in their offspring and is predictable based on the maternal titers of TSAb, with titers of >300% (normal <80%) indicating high risk for the neonate (4, 5). The presence of a combination of TSAb and TSH receptor (TSHR)-stimulator blocking antibodies (TSBAb) in the maternal circulation may lead to the development of late-onset neonatal Graves' disease (presenting later than 9 days post-partum) (8). Notably, TSBAb, when they occur alone (*i.e.* in the absence of TSAb), can rarely cause non-goitrous, non-autoimmune hypothyroidism (see below) (9). Graves' ophthalmopathy occurs in less than 50% of children with Graves' disease (6). Other manifestations of Graves' disease in children and adolescents include lid lag (resulting in the characteristic "stare"), goiter, tachycardia, hypertension, poor weight gain, irritability, jaundice and, in severe cases, cardiac failure.

The diagnosis of Graves' disease in the peripartum period is confirmed by detecting suppression of cord (or early post-natal) blood TSH levels in the presence of normal or elevated levels of serum total T_3 and total T_4 and high levels of free T_4 and free T_3. Neonatal Graves' disease usually resolves within 3 to 12 weeks, since maternal TSAb (of the IgG class) are degraded with a half-life of approximately 12 days (7). Treatment of neonatal hyperthyroidism includes sedatives, iodide such as Lugol's solution [one drop (8 mg of iodide), *tid*] or antithyroid drugs (methimazole, MMI, 0.5 mg/kg/day; or propylthiouracil, PTU, 5 mg/kg/day, divided in q 8 h dosing). Propanolol (1 mg/kg/day) or dexamethasone may also be helpful in relieving symptoms from autonomic dysfunction (due to hyperactivation of β-adrenergic receptors) and blocking the conversion of T_4 to the biologically more active T_3 (10, 11).

The differential diagnosis of Graves' disease in childhood includes other acquired causes, such as toxic adenoma, factitious hyperthyroidism, Hashitoxicosis, suppurative and non-suppurative thyroiditis and TSH-dependent hyperthyroidism due to a TSH-producing pituitary adenoma/tumor (TSH-oma). In newborns and infants, genetic causes of thyrotoxicosis should be excluded, such as familial congenital hyperthyroidism and TSH-dependent hyperthyroidism due to pituitary or generalized resistance to thyroid hormone (RTH) (12).

In childhood and adolescence, hyperthyroid patients can be very restless with deteriorating school performance, increased urinary frequency, heat intolerance and sometimes diarrhea (7). In post-pubertal girls, menstrual irregularities can be seen. The diagnosis of Graves' disease is made primarily on clinical grounds, *i.e.* the presence of goiter with a thrill, lid retraction, lid lag, tachycardia, palpitations, weight loss, heat intolerance, fatigue, tremor and hyperreflexia and is corroborated by the presence of an elevated serum free T_4, undetectable serum TSH and high titers of TSAb. In older children, an ^{123}I radioactive iodine (RAI) uptake measurement and scan may be required to rule out TH excess from thyroiditis or exogenous TH ingestion, in which cases the RAI uptake will be low or absent. In Graves' disease, the ^{123}I scan usually shows diffuse and vigorous uptake of the radionuclide by the thyroid gland. The activity of Graves' disease can be monitored by measuring TSAb levels over time (8).

In children with Graves' disease, clinical and biochemical euthyroidism can be achieved by treatment with moderate doses of antithyroidal drugs within 3 months, although occasionally progressively more aggressive treatment may be necessary for up to 2 years (7, 11). Before initiation of antithyroid drug treatment, a complete blood count (CBC) should be measured, since neutropenia may develop while on treatment (12, 13). Eventually, the therapy with antithyroidal medications is discontinued after 12-18 months, even in children who are well controlled on this therapy, in order to assess whether the disease has remitted. If a relapse of hyperthyroidism occurs after discontinuation of the antithyroidal drugs, it usually does so within the first year after discontinuation; unfortunately, this is the case in >70% of cases (10, 11). It has been suggested that lower rates of relapse of Graves' disease may be achieved by fully suppressing the thyroid gland with antithyroidals, while simultaneously maintaining these patients on levothyroxine (LT_4) therapy (14). However, this has been refuted in more recent extensive studies (15). Side-effects of antithyroidal medications include most commonly rash but also hepatitis, agranulocytosis and migratory arthralgias. Approximately 5% of children will develop one of these side-effects (12). Recently, treat-

ment of childhood-onset Graves' disease with PTU has been associated with a high prevalence of antineutrophil cytoplasmic antibody (ANCA) positivity and ANCA-related vasculitis and nephritis (16). The risk of development of side-effects from thionamides, as well as the reluctance of clinicians to use RAI ^{131}I for treatment of Graves' disease in children, render surgery (thyroidectomy) an attractive alternative therapy approach. In fact, this is usual practice in Europe, where many more thyroidectomies are performed in children for control of thyrotoxicosis compared to the situation in the United States (17). In childhood, indications for surgical treatment of thyrotoxicosis include non-compliance with medications, severe drug reactions, the diagnosis of toxic adenoma or an enlarging gland compromising the airway, esophagus or other local structures (nerves or vessels). However, caution needs to be exercised with regard to the possibility of development of serious post-operative complications, *i.e.* permanent hypoparathyroidism and recurrent laryngeal nerve paresis (17). Before surgery, Lugol solution or saturated solution of potassium iodide should be administered for 5-7 days to reduce the vascularity of the gland and acutely reduce TH secretion, along with β-blockers for symptomatic control. In cases of severe thyrotoxicosis, the pre-operative management should include the step-wise addition of iopanoic acid or ipodate, high-dose PTU therapy, glucocorticoids and, very rarely, lithium carbonate. Currently, ^{131}I therapy in children is being used more frequently than in the past but still predominantly after the onset of puberty. The ^{131}I therapy doses in Graves' disease aim at the delivery of the following ranges of activities in the hyperfunctioning gland: 80-125 μCi/g of tissue if the aim is to preserve some residual thyroidal function post-therapy, or 125-200 μCi/g of tissue if the aim is to completely ablate the gland (13). Authorities currently recommend the administration of ^{131}I therapy doses at the higher range (thyroid ablative). The avoidance of ^{131}I therapy for Graves' disease in early and mid-childhood is based on concerns about the potential carcinogenic effect of ^{131}I therapy on the thyroid glands of younger children, should they receive such therapy during the growth phase of the gland (18).

In addition to Graves' disease caused by transplacental transfer of maternal TSAb, neonatal hyperthyroidism can be caused by germline constitutively activating mutations of the TSHR, leading to autosomal dominant non-autoimmune hyperthyroidism (19, 20). Surgically removed thyroid glands in these patients demonstrate diffuse hyperplasia without lymphocytic infiltration. The onset of thyrotoxic symptoms and signs commonly occur in the neonatal period. The diagnosis is established by the presence of a positive family history, in combination with mutation analysis of the TSHR, as well as the biochemical findings of a suppressed serum TSH level, increased serum total T_4 and free T_4 levels and negative antithyroidal antibodies (ATA) and TSAb (19, 20). Affected individuals with this disorder present with the typical symptoms and signs of hyperthyroidism, including goiter. These hyperthyroid patients are difficult to treat medically with antithyroidal drugs, β-blockers and dexamethasone and, hence, may present with premature craniosynostosis (21). For these reasons, early thyroidectomy has been recommended (21).

Another cause of hyperthyroidism in childhood is thyroiditis. Chronic lymphocytic thyroiditis in its goitrous variant, *i.e.* Hashimoto's thyroiditis (HT), is the most common form of thyroiditis in childhood and adolescence (2). HT is associated with other autoimmune diseases. In fact, 40% of children and adolescents with Type 1 diabetes mellitus have clinical or biochemical evidence of HT (22). Notably, HT most commonly leads to hypothyroidism and only rarely to thyrotoxicosis, the so-called "Hashitoxicosis". This clinical entity develops during the destruction of thyroid follicles caused by intense inflammation, with subsequent "colloid leak" and uncontrolled release of (occasionally large) amounts of preformed TH which is already stored in the gland. Occasionally, Hashitoxicosis (and HT in general) may be accompanied by the formation of lymphocytic nodules and, hence, needs to be differentiated clinically from a hyperfunctioning uninodular adenoma (see below). Other forms of thyrotoxic thyroiditis are non-suppurative subacute thyroiditis (SAT) and acute suppurative thyroiditis.

SAT (or de Quervain's thyroiditis) occurs rarely during childhood and adolescence but becomes much more common between the 2nd and 5th decades of life, predominantly in women (23). The disease is usually preceded by a viral illness with the manifestations of sore throat, fever, neck pain and a tender thyroid gland. A few children may have minimal symptoms and signs, thus making it difficult to differentiate this type of thyroiditis from HT (12, 23). Causative pathogens reported in SAT include the mumps virus, measles, influenza, adenovirus, Coxsackie virus, the common cold viruses, Epstein-Barr virus, cat-scratch disease, sarcoidosis, Q fever, streptococcal infections and others (12). Although children are frequently exposed to and infected with viral illnesses, SAT is rare in childhood. Only 5% of all patients with this disease reported in the literature were younger than 20 years of age and only 8 of all these patients were younger than 13 years of age (12). However, it is possible that this disorder may be under-recognized and/or erroneously classified, mainly due to the common practice

of avoiding the performance of RAI scans and uptake measurements in children. Laboratory studies reveal a suppressed serum TSH, elevated free T_4 and/or total T_3 levels, in a fashion similar to other hyperthyroid states. However, in SAT the 24-h RAI uptake is characteristically low, reflecting the diffuse damage to the thyroid gland with its inability to trap and retain iodine. Early in the disease course, the erythrocyte sedimentation rate (ESR) is elevated, as are the α_2- and γ-globulin levels, reflecting an acute inflammatory state (24). If the test of RAI uptake is not performed, the differential diagnosis can be problematic. Surreptitious ingestion of excessive amounts of exogenous TH can be differentiated from thyrotoxic thyroiditides by the presence of undetectable serum TG levels in combination with a low RAI uptake, undetectable ATA and TSAb, elevated serum free T_4 or total T_3 levels and low serum TSH (2).

The clinical course of SAT varies widely but can generally be divided into an acute stage of hyperthyroidism, lasting from 2 to 6 weeks, a stage of euthyroidism and a recovery stage with elevation of TSH and hypothyroidism generally lasting from 2 to 7 months. Rarely, persistent hypothyroidism ensues (12, 23). Because SAT runs a benign and self-limiting course, only symptomatic treatment is advised. Such therapy may consist of the administration of aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) to alleviate the local pain/discomfort. Sometimes, prednisone (0.5 mg/kg/day given for one week) may be needed, if aspirin or NSAIDs cannot be given or prove to be unhelpful. Propanolol or other β-blockers can also be administered, especially if severe adrenergic symptoms of hyperthyroidism develop. If hypothyroidism eventually ensues, therapy with LT_4 may become necessary, with the intention to eventually taper the LT_4 dose and assess the recovery of the thyroid gland within a few months.

Acute suppurative thyroiditis has become quite rare since the introduction of antibiotics more than half a century ago. Over the last 2 decades, most cases have been reported from Japan (25, 26). Since the thyroid gland is encapsulated and has a high iodine content, *i.e.* conditions that are unfavorable for bacterial invasion and proliferation, suppurative infection of the thyroid occurs only rarely. Infectious routes in cases of suppurative thyroiditis include inoculation of thyroidal tissue through vascular or lymphatic routes, as well as direct extension from an internal fistula or infected parathyroid cyst. Prior to the 1950s, the causative organism usually was hemolytic *Streptococcus* (27). Now, the major pathogens include *Staphylococcus aureus* and *S. pneumoniae* (25, 27). Both genders and both lobes are equally affected. Children with suppurative thyroiditis often experience sudden unilateral pain that radiates to the ears, mandible or occiput. The thyroid gland is typically tender and can be fluctuant on palpation. Sore throat, hoarseness and dysphagia, usually of rapid onset, may also be present. Hyperthyroidism is not common. Laboratory studies typically show intense leukocytosis with a "shift to the left", an elevated ESR, normal or elevated serum free T_4 and total T_3 levels, normal or low serum TSH, and a normal or low 24-h RAI uptake (12, 25, 27). For definitive diagnosis, a fine needle aspiration (FNA) of the affected thyroid area should be performed for Gram stain and culture. Thyroid ultrasonography should be done to evaluate for potential abscess formation, in order to timely intervene surgically. Early parenteral antibiotic treatment (penicillin, ampicillin or cephalosporines, accompanied by adequate anaerobic coverage) is essential, since most untreated patients develop an abscess. In certain cases, complete excision of the abscess by lobectomy or more extensive operations may be indicated. If a fistula is the causative pathology, complete extirpation thereof is essential. In most patients, thyroid function remains normal post-operatively and full recovery is expected. A comprehensive list of non-endocrine conditions that need to be considered in the differential diagnosis of thyrotoxic thyroiditis in children and adolescents is shown in Table 1.

Other causes of hyperthyroidism in childhood include pituitary and generalized RTH, as well as TSHomas (28-30). These conditions are extraordinarily rare and can usually be distinguished from other much more common functional thyroid disorders by the TRH-stimulation test, measurement of serum levels of the pituitary glycoprotein α-subunit (α-SU) and the α-SU/TSH ratio as well as the performance of pituitary magnetic resonance imaging (MRI) (28, 30). The post-TRH response of serum TSH is characteristically "flat" in TSHomas, especially in patients who have undergone prior thyroidectomy and/or ^{131}I thyroidal ablation (30). With improving biochemical assays and imaging modalities, TSHomas are now more readily diagnosed; they occur extremely rarely in children. Primary therapy for TSHomas consists of transsphenoidal surgery. Treatment with long-acting somatostatin analogs [octreotide, lanreotide and their newer depot (LAR) forms], as well as external beam pituitary irradiation, may become necessary for control of tumoral TSH hypersecretion and growth (30). Patients with the syndrome of RTH may be managed with β-blockers, especially for symptomatic control of cardiac thyrotoxicosis, as well as therapy with high-dose triiodothyronine (LT_3), which has lead to anecdotal improvement in RTH-associated neurobehav-

Table 1 - *Differential diagnostic considerations in acute thyrotoxic thyroiditis (hashitoxicosis, subacute thyroiditis, and suppurative thyroiditis) in children and adolescents.*

Cervical adenitis and myositis
Pharyngitis
Tonsillitis
Otitis media and externa
Dental caries and abscess
Hemorrhage into thyroid nodule or cyst
Infected thyroglossal duct cyst
Graves' disease
Iodine-induced thyrotoxicosis
Follicular adenoma
Temporomandibular joint syndrome
Thyroid cancer

ioral symptoms, including attention deficit-hyperactivity disorder (ADHD) (29).

Hyperfunctioning thyroid adenomas in children are quite rare and usually result in clinical and biochemical hyperthyroidism, especially when they are larger than 2.5 cm (31). Typically, a RAI scan shows uptake exclusively in the adenomatous tissue with suppression of uptake in the rest of the gland. Serum TSH is undetectable, in the presence of high serum levels of total T_3 and free T_4. Occasionally, only the serum levels of total T_3 and/or free T_3 are elevated, in the context of the so-called "T_3-toxicosis" syndrome. Since the adenoma is encapsulated, surgery is rarely risky and the therapy of choice, since it is curative upon removal of the adenoma. ^{131}I administration is usually avoided in children with toxic adenomas, as the ^{131}I therapy doses required for ablation of these adenomas are quite high (500-1500 μCi/g of tissue, depending on the 24-h percent RAI uptake, with the average mass of these adenomas being >30 g) (J.C. Reynolds, personal communication).

Exogenous causes of hyperthyroidism in children and adolescents include accidental or intentional intake of TH. In adolescents, psychiatric disease or disorders of dietary intake (bulimia/anorexia nervosa) may lead to excessive ingestion of TH (32). This may result in the erroneous diagnoses of Graves' disease or thyrotoxic thyroiditis. However, exogenous TH intake leads to an almost pathognomonic constellation of features, including an undetectable serum thyroglobulin (TG) TG level in association with a low RAI uptake, as opposed to the situation in Graves' disease or thyrotoxic thyroiditis, *i.e.* disorders that typically manifest with high serum TG levels.

Hypothyroidism

Hypofunction of the thyroid gland in children can have severe and permanent sequelae, especially during the sensitive time periods of brain development and skeletal growth and maturation. The prognosis of children with congenital hypothyroidism has improved with the introduction of neonatal screening (capillary blood TSH and total T_4 or free T_4 levels) and subsequent institution of therapy in a more timely manner (33-35). In this screening procedure, a capillary blood TSH value >40 mU/l in the early post-natal period is regarded as abnormal. The incidence of congenital hypothyroidism varies with the geographic area, being reported as high as 1/3300 live births (l.b.) in Europe and as low as 1/5700 l.b. in Japan but averaging 1/4500 l.b. in most other areas (36).

Congenital hypothyroidism may be transient, *i.e.* may disappear spontaneously. Its etiology can be diverse and includes: thyroid agenesis/dysgenesis (in some cases associated with germline mutations in transcription factors that regulate thyroid embryogenesis) (37-39); transplacental passage of maternal TSBAb (9, 40); maternal use of antithyroid drugs (41); maternal iodine deficiency (42); enzymatic defects in the thyroid hormonogenetic pathways (43-45); hypothalamic or pituitary hormone deficiency [including panhypopituitarism, the presence of mutations in the β-subunit of TSH (46) and Pit-1 deficiency (47)]; and TSH resistance (usually, although not always, associated with mutations in the extracellular domain of the TSHR) (39, 48). The incidence of transient congenital hypothyroidism varies depending on the method of screening, age at screening and its definition. Approximate prevalences in the neonatal period for the various thyroid disorders that can lead to neonatal hypothyroidism are: 1:4000 for thyroid dysgenesis, 1:30,000 for dyshormonogenetic disorders and TSH resistance, 1:100,000 for hypothalamic-pituitary disorders, and 1:40,000 for transient hypothyroidism [*i.e.* drug-induced, maternal antibody (TSBAb)-induced and idiopathic] (49). Screening for congenital hypothyroidism should already begin during pregnancy, since even mild maternal hypothyroidism impacts on full achievement of the intelligence and behavioral genetic potential in the offspring (50).

In order to distinguish between permanent and transient congenital hypothyroidism, thyroid RAI imaging at diagnosis is recommended. Thyroid dysgenesis may include true agenesis of the gland, ectopically located thyroid tissue and thyroid hypoplasia, all of which can be distinguished by RAI (^{131}I or ^{123}I) ^{99m}Tc scan (51).

Infants with congenital hypothyroidism, even if transient, should be treated to reach a serum total T_4 val-

ue of >10 μg/dl within 2 weeks after treatment initiation. In some infants/children, the serum total T_4 concentrations may reach a level of 17 μg/dl before serum TSH values decrease within the normal range (51). In cases of severe iodine deficiency, which can be easily assessed by measuring urinary 24-h iodine excretion, congenital hypothyroidism can be treated by iodine supplementation alone (52).

Symptoms and signs of hypothyroidism in neonates and infants may be variable. If prolonged intra-uterine hypothyroidism is present, *i.e.* due to exposure to large amounts of TSBAb throughout gestation, thyroid agenesis or complete defects in thyroid hormonogenesis, neonates often can present clinically with hypothermia, poor feeding behavior, severe bradycardia, umbilical hernia, and prolonged (>3 days) jaundice. However, most infants are diagnosed only biochemically, *i.e.* via neonatal screening of TSH and/or total T_4, since clinical manifestations may not appear until 2 months of age. If serum TSH is >40 mU/l or total T_4 <6 μg/dl, treatment with LT_4 should be initiated immediately. If serum TSH is between 20 and 39 mU/l and $T_4 \geq 6$ μg/dl, LT_4 therapy may be delayed until results from additional biochemical and imaging tests become available. Thyroid RAI of ^{99m}Tc imaging should be performed. The initial dose of LT_4 ranges from 10 to 15 μg/kg/day (53). This translates into a daily dose of approximately 50 μg of LT_4 in a full-term infant. The LT_4 dose should be titrated according to the serum TSH and free T_4 values, which should be measured after 7, 14 and 28 days of therapy (53, 54). Serum free T_4 is best measured by equilibrium dialysis, since TBG or TBPA abnormalities may exist in the neonate. Notably, oral (liquid) LT_4 should be administered apart from any calcium-, soy- and iron-containing preparations or medications, *i.e.* about 2 h apart from any feeding. Serum T_4 and free T_4 concentrations during the first year of life in normal infants are higher than those in children and adults, with serum T_4 values as high as 16 μg/dl (55). Along with the regular follow-up of thyroid function tests in these infants/children, their growth should also be periodically assessed by plotting height and weight on a normative chart.

Acquired hypothyroidism after the immediate neonatal period, *i.e.* in late infants, children and adolescents, has many causes and variable clinical manifestations. These are summarized in Table 2. If the onset is after age 2, central nervous system (CNS) function will probably not be permanently impaired but detrimental consequences may still occur on growth and development, up until completion of puberty (56, 57).

Primary hypothyroidism is more common than central (secondary) hypothyroidism. The most common cause worldwide is iodine deficiency. Second ranks chronic autoimmune thyroiditis, with its two subtypes, *i.e.* goitrous thyroiditis (or HT), and atrophic thyroiditis (58). The incidence of HT peaks in midpuberty. This disorder can be usually diagnosed by the presence of high serum titers of ATA, namely antithyroid peroxidase (anti-TPO) or anti-Tg antibodies. Anti-TPO antibodies may directly block iodine organification (59) and, thus, play a pathogenetic role in the development of thyroid failure in patients with HT. Moreover, thyroid failure with autoimmune basis may occur in association with other autoimmune disorders of greater severity, such as systemic lupus erythematosus and juvenile rheumatoid arthritis (60), as well as within the realm of the autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) syndrome [also called APS-1 and linked to recently identified mutations in the AIRE (or autoimmune regulator) gene] (61, 62). In older children and adolescents, destruction of the thyroid gland due to external radiation has been documented as an important cause of thyroid failure. This has been observed in the context of irradiation given for medical purposes (for the therapy of lymphoma or posterior fossa brain tumors), as well as exposure to large doses of radioactive environmental contamination, such as those seen after the Chernobyl nuclear reactor accident in 1986 (63, 64). In these cases, hypothyroidism may occur as early as one year after radia-

Table 2 - *Etiology of acquired hypothyroidism in children and adolescents.*

Central (hypothalamic-pituitary) hypothyroidism
Multiple pituitary hormone deficiencies
Idiopathic (non-familial)
Hypothalamic or pituitary tumors
Midline central nervous system defects
Post-treatment of brain and other tumors
Surgery
Radiation
Primary hypothyroidism
Endemic goiter
Chronic autoimmune thyroiditis
Goitrous autoimmune thyroiditis (Hashimoto's thyroiditis)
Atrophic thyroiditis
Drug-induced hypothyroidism (lithium, iodide, carbimazole, methimazole, propylthiouracil)
Goitrogen ingestion
Thyroidectomy
Partial/late onset dyshormonogenetic defects
History of thyroidal irradiation
External irradiation
Radioiodine (^{131}I) therapy

tion. Even in "apparently sporadic" cases of primary hypothyroidism that develop after the neonatal period, the potential for the presence of an inherited disorder should be sought, as some patients with familial syndromes, including those with generalized RTH, may be missed.

In children with primary hypothyroidism, serum TSH values are usually >50 mU/l, in association with low serum free T_4 concentrations. Notably, total T_3 or free T_3 measurements are not helpful in the establishment of the diagnosis of hypothyroidism. If the time of onset of hypothyroidism is unclear, determination of the bone age can prove useful in its approximate estimation. Thyroid imaging by ultrasound or RAI scanning is rarely indicated in patients with primary hypothyroidism and predominantly indicated only for children with a thyroid nodule who have been previously exposed to radiation (65). A recently described cause of hypothyroidism is thought to be due to "hypersensitivity" of the HPT axis feedback mechanism (66), although the molecular basis of this defect remains unknown.

Central (or secondary) hypothyroidism, *i.e.* thyroid dysfunction due to TRH or TSH deficiency, occurs rarely during childhood and adolescence. It usually induces minimal or absent signs and symptoms of hypothyroidism, except for growth retardation.

Characteristically, serum TSH is low or normal in the face of a frankly low serum free T_4 level. In some patients with hypothalamic hypothyroidism, TSH concentrations may be as high as 20 mU/l, due to the presence of bio-inactive TSH molecules (which remain, however, immunoreactive in immunology-based TSH detection and measurement assay systems) (2). MRI of the pituitary is recommended for all patients with central hypothyroidism to exclude serious intracranial pathology, such as infiltrative disorders (*i.e.* sarcoidosis or histiocytosis-X) and CNS tumors (67). Survivors of childhood cancer who have been cranially irradiated may have latent (or "hidden") central hypothyroidism (68). A major cause of congenital, non-inherited central hypothyroidism include syndromes with midline anomalies, *e.g.* holoprosencephaly. Acquired causes of central hypothyroidism include CNS tumors, such as craniopharyngiomas, gliomas and others. A TRH-stimulation test usually shows either an absent TSH rise in response to TRH or a delayed, yet normal-amplitude, TSH peak (67).

Infants aged 6 months to 3 years who have acquired hypothyroidism have similar symptoms and signs to those with untreated congenital hypothyroidism (2). Two of the most striking features of early acquired hypothyroidism are a deceleration of linear growth during the end of the first year of life and a delay in developmental milestones. Other features may include macroglossia and umbilical hernia. Children from age 3 to adolescence who suffer from acquired hypothyroidism do not usually have permanent impairment of their CNS function if they are treated adequately immediately after diagnosis (56). However, similarly to younger infants, these older children may demonstrate growth retardation with delayed skeletal maturation. Moreover, these patients may have delayed dental development, myopathy with weakness, fatigue, decrease in school performance, muscular pseudohypertrophy (Kocher-Debré-Semelaigne) syndrome and hyperprolactinemia without galactorrhea (58). During adolescence, acquired hypothyroidism is typically mild, with most patients showing only a goiter. In severe cases, puberty can be delayed. Affected adolescents present with non-specific complaints, which are typical even of normal individuals in this age group, including fatigue and headaches. After the onset of puberty, newly hypothyroid adolescents experience a delay in pubertal development, including delayed menarche (girls) and facial hair growth (boys), as well as galactorrhea. Rapid linear growth during adolescence is often attenuated by hypothyroidism. Characteristically, growth accelerates again after initiation of LT_4 therapy (69).

LT_4 treatment for hypothyroidism should be given once daily and apart from calcium or iron preparations or foods. Late infants usually need 4-8 μg/kg/day of LT_4, whereas children and adolescents can start with 2-4 μg/kg/day (approximately 25-50 μg) of LT_4 for the first 4 weeks. The dose can be subsequently increased by 25 μg/day every 4-6 weeks until normalization of TSH occurs (69). Usually, the "target" serum total T_4 and/or free T_4 values should be at the upper half of the normal range for age. Excessive LT_4 therapy in late infants and children may advance bone maturation and lead to restlessness, insomnia and, occasionally, benign intracranial hypertension. If the child remains clinically euthyroid with a normal/adequate linear growth, the dose can be maintained at the chosen "target" level.

STRUCTURAL DISORDERS OF THE THYROID GLAND IN CHILDHOOD AND ADOLESCENCE

Developmental anomalies

Several inborn errors of TH synthesis and metabolism may lead to early goiter formation. These disorders are rare with the exception of Pendred's syndrome, which occurs with an incidence of 1:50,000 l.b. Pendred's syndrome is an autosomal recessive inherited disorder with the clinical manifestations of profound sensorineural deafness of early onset, de-

fective iodine organification, goiter, and hypoplasia of the cochlea (70). Overt hypothyroidism may also rarely develop in patients with this syndrome. The molecular basis of Pendred's syndrome has been recently identified as mutation(s) in the *PDS* gene, which encodes pendrin (71). Other inherited abnormalities associated with goiter include: iodide transport defects (associated with mutations in the sodium/iodide (Na^+/I^-) symporter (NIS) (45), organification defects other than Pendred's syndrome, defects in TG synthesis and processing, iodotyrosine synthesis and coupling defects, RTH (28), and autosomal dominant non-autoimmune hyperthyroidism (20). Most of these disorders will cause either hypothyroidism or thyrotoxicosis in addition to thyromegaly, and, hence, have been discussed in previous sections.

Other inborn errors of TH synthesis and metabolism can be associated with thyroid dysgenesis/agenesis. Thus, familial TSH deficiency (46), Pit-1 deficiency (47), and TSH unresponsiveness/resistance, as well as inherited disorders due to mutations in nuclear transcription factors, such as thyroid-specific transcription factor-2 (TTF-2) and Pax8 (37, 38), can result in thyroid dysgenesis/agenesis. More specifically, thyroid ectopy is usually diagnosed early in life due to the associated thyroid failure but may rarely present for the first time in adolescence (72). In most of the above disorders, the thyroid structural anomalies are accompanied by hypothyroidism and have been presented in previous sections.

Except for familial non-autoimmune hyperthyroidism and RTH, which are autosomal dominant disorders, all the above structural abnormalities show an autosomal recessive mode of inheritance. Notably, however, 30-40% of RTH cases (46) and a significant proportion of cases of idiopathic thyroid dysgenesis/agenesis occur sporadically, probably as a result of *de novo* mutations.

Thyroid nodules

During the first two decades of life thyroid nodules are uncommon, with a multinodular gland most commonly caused by HT. However, isolated discrete thyroid nodules are rare in HT. Nodule formation can also occur in association with thyroid hyperstimulation by TSH or TSAb, as seen in iodopenic goiter and Graves' disease respectively (73). All nodules should be examined further to exclude a cyst *vs* a benign or malignant tumor. This is especially important in patients with a history of previous exposure to ionizing radiation in the head and neck or high-dose total body irradiation (74-78). Furthermore, a positive family history for thyroid cancer [*e.g.* medullary thyroid carcinoma (MTC), papillary thyroid carcinoma (PTC)] is also essential to elicit (79, 80).

A careful physical examination of the head and neck should be performed, keeping in mind that a hard nodule could indicate calcification, whereas a smooth nodule often points to the presence of cystic elements. Tender nodules may stem from hemorrhage into a cyst or mass. Lymph nodes should be palpated carefully, spanning the area from the posterior cervical triangle to the suprasternal notch and supraclavicular fossae. Thyroid ultrasonography is more sensitive than physical examination in detecting nodules and, thus, recommended for virtually all patients but especially those who had formerly been exposed to ionizing radiation or have family history of thyroid neoplasia (75, 78, 81). A cyst could be further subjected to fine needle aspiration (FNA), which in this case may also be "therapeutic" with collapse of the cyst walls, or surgically removed. In infants and children, it is debatable whether thyroid nodules should be immediately explored via an excisional biopsy rather than be subjected first to FNA biopsy (82). There are obvious technical limitations in "blind" and ultrasonographically guided FNA biopsies in children younger than 12 years. Hence, in younger children, an excisional biopsy should be considered as the first step in the diagnostic algorithm (83). However, in adolescents, an ultrasound-guided FNA biopsy may be justified as the first diagnostic test of choice, depending on their understanding of the procedure and compliance by the patient at the time of biopsy. A competent cytopathologist with experience in the interpretation of thyroid FNA specimens can be invaluable in aiding the clinician with decision-making. Unfortunately, the existence of paucicellular samples, a small percentage of cytologically adequate samples that are falsely designated as "negative for malignancy" and the cytologic diagnostic categories of "follicular lesion", "follicular neoplasm", and "lesion suspicious for malignancy", reflect persistent problems with the optimal interpretation of FNA biopsies (84). In children, about 75% of thyroid nodules that are investigated using FNA biopsy are benign, with a diagnostic accuracy for the FNA technique of about 90% (82).

Prior to the biopsy (FNA or excisional) of a nodule, thyroid function tests should be checked to exclude the diagnosis of a hyperfunctioning solitary adenoma ("hot nodule"). In case of the latter diagnosis, the presence of elevated serum free T_4 and total T_3 levels, and a suppressed serum TSH will prompt the performance of a RAI (^{123}I) scan. As almost all "hot nodules" are benign, there is no need for biopsy but rather proceeding directly with treatment of this condition. Usually, these hyperfunctioning adenomas are surgically excised, especially if clinical thyrotoxic symptoms and signs develop (31, 85). With

the exception of "hot nodules", in thyroid uninodular disease, thyroid function tests are typically normal and ATA titers are negative. If a RAI scan is performed prior to the biopsy of a nodule in non-hyperthyroid patients, this will commonly demonstrate a lesion which does not concentrate RAI ("cold nodule"). This finding may raise the suspicion for malignancy, although, even in children, >75-80% of "cold nodules" are benign (83).
Patients with a history of irradiation should be placed on LT_4 therapy prophylactically at doses adequate to suppress the TSH level, and thereby lower the risk of radiation-induced nodule formation. If these patients develop a thyroid nodule, immediate excisional biopsy (or in older children and adolescents an FNA biopsy) is recommended. This should be perfomed and interpreted with a much more increased level of suspicion of malignancy in these patients *vs* those without history of neck irradiation.

Thyroid cancer

Epidemiology and classification

Thyroid carcinomas in childhood are rare, accounting for 1.5% of all tumors before the age of 15 and 7% of the tumors of the head and neck during childhood. There is a definite female predominance, with 2/3 of these malignancies occurring in girls (86). Thyroid cancer is broadly classified into well-differentiated, poorly-differentiated and undifferentiated carcinomas. Malignant transformation of the thyroid follicular epithelium (of mesodermal origin) gives rise to papillary (PTC), follicular (FTC), and anaplastic thyroid cancers (ATC). MTC arise from the malignant transformation of the parafollicular (or C-) cells of the thyroid, which are of neuroectodermal origin and produce calcitonin. Thyroid lymphomas and metastases to the thyroid from cancers of other organs, such as kidney, lung, or breast, are very rarely found in children (87). Most PTC and FTC are well-differentiated malignancies, capable of secreting TG, which may be detectable in the peripheral circulation. PTC accounts for 85-90% of thyroid cancer cases in childhood, followed by MTC which accounts for about 5% of cases. FTC is rare in childhood and occurs predominantly in older children and adolescents. Finally, ATC is exceptionally uncommon in children and adolescents.

Pathogenesis – risk factors

Risk factors for the development of PTC, FTC and ATC include: exposure to ionizing radiation (especially in younger children), iodine deficiency and other conditions associated with prolonged and sustained elevation of serum TSH, as well as autoimmune disorders, such as Graves' disease and HT (87). From a standpoint of molecular genetics, thyroid cancer can be a part of the manifestations of several inherited syndromes, including familial PTC, Carney complex, Gardner's and Peutz-Jeghers' syndromes, Cowden's disease (80, 88-90), as well as multiple endocrine neoplasia type-2 (MEN-2) (the latter relevant to MTC alone) (79). Thyroid cancer has also been reported in one child with the McCune-Albright syndrome (91).

Clinical failures – diagnosis

Children and adolescents with thyroid cancer most commonly present with anterior cervical lymphadenopathy. The combination of lymphadenopathy and a palpable thyroid nodule occurs in about 50% of children with thyroid cancer. Affected patients are typically euthyroid. Rapidly developing dysphagia, dyspnea, stridor or dysphonia are indications of expansive growth (92). The physical examination should be also directed to the recognition of signs of a possible genetic syndrome, such as MEN-2.
The diagnosis of thyroid cancer in children and adolescents is established by either an FNA biopsy or (in younger children) an open, excisional biopsy of a thyroid nodule and/or cervical lymph node. PTC and FTC may secrete large amounts of TG, which, however, may also be produced in excessive amounts by large goiters and, thus, be of limited value in differential diagnosis during initial presentation (93). Baseline plasma calcitonin levels may be elevated in children with MTC. If the baseline calcitonin levels are normal, an iv calcium or pentagastrin stimulation test may show an abnormal calcitonin response in a child with MTC or C-cell hyperplasia (79, 94, 95). In order to exclude metastases after the diagnosis is established, chest radiographs should be performed in almost all cases. Along similar lines, computed tomography and/or MRI of the neck, mediastinum and chest may also be used at the time of diagnosis, depending on the case. Thyroid scintigrams using either ^{123}I or ^{99m}Tc usually show perinodular parenchyma with normal 24-h RAI percent uptake, as well as one or more "cold" (or hypofunctioning) nodules. Discrepancies between scintigrams taken with ^{123}I or ^{99m}Tc can occur. Because a carcinoma can appear on scanning as "hot" with ^{99m}Tc and "cold" with ^{123}I, patients with the former finding who are not hyperthyroid require repeat scanning with RAI (96). ^{111}In-octreotide (Octreoscan®) scintigraphy appears useful specifically for the detection of MTC (97). Very small nodules may not be imaged by any of the above tech-

niques, yet may be detectable by an ultrasonographic examination of the thyroid gland. In pediatric patients, thyroid ultrasonography is currently routinely recommended as one of the first studies that should be obtained in the evaluation of a thyroid nodule(s).

Treatment: surgery, ^{131}I, TH suppressive therapy

Total or near-total thyroidectomy is the initial treatment of choice for children and adolescents with thyroid cancer (PTC, FTC). It should be carried out by an endocrine, oncologic or head and neck surgeon, preferably with considerable pediatric expertise, to minimize the risk of post-operative complications, such as recurrent laryngeal nerve injury and permanent hypoparathyroidism (98, 99). By performing total thyroidectomy, subsequent RAI (^{131}I) ablation of the thyroid remnant is greatly facilitated. Remnant ablation therapy impacts positively on prolonging disease-free intervals. RAI therapy has also been shown to decrease disease-specific mortality in adults with thyroid cancer but similar data are not rigorously validated in children (100). Total/near-total thyroidectomy is typically accompanied by central cervical compartment limited dissection for inspection of the locoregional lymph nodes in levels II and III of this compartment. More extensive operations, such as modified radical neck dissections, are very rarely indicated (usually in the presence of bulky disease invading neck soft tissues) and are generally to be avoided in children with PTC/FTC.

Within 4-6 weeks after thyroidectomy, children and adolescents should be evaluated for residual thyroid tissue (remnant) by a RAI (0.5-2 mCi of ^{131}I or 500-2000 μCi of ^{123}I) diagnostic whole-body scan (WBS) in order to pursue ^{131}I ablative therapy immediately afterwards. Serum TSH should exceed 30 mU/l before RAI WBS to receive obtain meaningful results and ensure an effective RAI therapy (101). Because more than 10% of children with thyroid cancer (in comparison to 2% of adults) have disseminated (mostly lung) at the time of initial diagnosis, the RAI WBS is especially useful in revealing these sites of disease prior to therapy, as these metastases may not be apparent on chest radiographs. Along these lines, ^{131}I therapy is generally recommended after thyroidectomy for all children with thyroid cancer. If no disease is seen outside the thyroid bed by RAI diagnostic WBS, ^{131}I is administered for ablation of any normal thyroid remnant. This is required to eliminate thyroid function and also facilitates the use of TG as a tumor marker for recurrent disease during periodic follow-up (102). ^{131}I doses for ablation vary. A single administration of about 29 mCi is sufficient for thyroid bed destruction in >50-60% of adults with thyroid cancer. This dose should be sufficient for children who are generally more sensitive to radiation than adults and are at risk for developing secondary cancers over a much longer projected life expectancy following RAI treatment *vs* adult patients. If cervical lymph node or pulmonary metastases exist at the time of the first RAI therapy, much higher doses (150-200 mCi) of ^{131}I are required, having as an aim not only the ablation of the remnant but also the eradication of metastatic disease (103). Five to seven days after ^{131}I therapy, another WBS should be performed to monitor the sites of uptake of the therapy dose (104).

Following remnant ablation, all patients should be given LT_4 at doses sufficient to induce suppression of serum TSH, *i.e.* 2.1-2.5 μg/kg/day (depending on the patient's age). This TH suppressive therapy (THST) eliminates any growth-promoting effects of TSH on malignant thyroid cells. Side-effects of THST, which typically causes subclinical (mild) iatrogenic hyperthyroidism, include vascular headaches in children and adolescents from age 8 to 20, insomnia, attention deficits (that may persist for long-term), as well as deleterious effects on skeletal maturation and calcification with subsequent osteopenia. In most cases, the TSH target range is 0.1-0.4 mU/l, although some children with clinically more aggressive disease require full suppression of their serum TSH to undetectable levels, *i.e.* <0.02-0.05 mU/l (105).

Follow-up of patients and treatment of residual/recurrent disease

Regular monitoring of patients with thyroid cancer is very important and should be a life-long endeavor. Specifically, the first follow-up evaluation, usually at 6 months after the initial RAI therapy (given for remnant ablation), is of great importance. During this follow-up, patients should be evaluated under conditions of stimulated TSH and undergo a RAI diagnostic WBS. Adequate TSH elevation is achieved by TH withdrawal, starting approximately 6 weeks before the diagnostic WBS is performed. During the hypothyroid preparatory period, the patient is allowed to take liothyronine (LT_3) for the first 4 weeks to ameliorate symptoms of myxedema. LT_3 must be stopped 2 weeks before undergoing scanning; during the same period a low-iodine diet (LID) is instituted, rendering any residual thyroid tissue highly avid for the uptake of a therapy dose of ^{131}I (106). If the diagnostic RAI WBS is negative, which corresponds to a total thyroid bed 48-h RAI percent uptake of <0.3%, thyroid ablation has been successful. This occurs in approximately 80% of the cases.

In these cases, the stimulated serum TG (under hypothyroid conditions) is either undetectable or very low (<2 ng/ml). In the remaining 20% of cases, either a proportion of the remnant had escaped full initial ablation or metastatic disease exists. Typically, in these patients, the stimulated serum TG (under hypothyroid conditions) is well above 10 ng/ml. This is accompanied in up to 65-70% of cases by an abnormal (positive) diagnostic WBS, which delineates the number and approximate sites of residual thyroid tissue (107). If ^{131}I treatment is administered, a post-therapy WBS should also be performed for further localization of metastases. In-between follow-up evaluations, patients should be maintained on THST with LT_4.

Patients who are considered to be in a status of no evidence of disease (NED) after their first post-ablation evaluation should be evaluated with a RAI diagnostic WBS and serum TG measurements every 6-9 months for the subsequent 2 years. This can be achieved either by TH withdrawal or by the administration of recombinant human (rh)TSH (Thyrogen®). In patients who remain in NED status, the TSH-stimulated diagnostic RAI WBS remains negative and stimulated serum TG levels remain <10 ng/ml (under hypothyroid conditions) (107) or <2 ng/ml (after rhTSH administration). Following this series of follow-up evaluations, at least annual physical examination and measurement of serum TG levels while on THST are required. If at the time of one of these evaluations the serum TG level becomes detectable while the patient is on THST, repeat diagnostic RAI WBS and serum TG measurement under hypothyroid conditions are indicated, in preparation for probable ^{131}I treatment.

In the minority of patients who will continue to harbor residual disease after the initial two ^{131}I treatments or develop recurrent disease at any time during their long-term follow-up, additional ^{131}I therapies need to be administered for eradication of metastatic disease. In these patients, standard, fixed ^{131}I therapy doses (up to 200 mCi/administration) may be given every 6 months (103). Alternatively, the maximal safe dose may be calculated by pre-treatment whole body and blood dosimetry (108, 109). In some patients with persistent/ recurrent metastatic disease, the TSH-stimulated RAI WBS under hypothyroid conditions will be negative, despite concomitantly detected elevations in serum TG levels (≥10 ng/ml). These "scan negative-TG positive" patients should undergo at least one more high-dose ^{131}I treatment. Indeed, many of them may require additional treatments if the post-therapy ^{131}I scans remain positive in the face of persistent hyperthyroglobulinemia.

With repeated therapies, the side-effects of ^{131}I need to be considered. These include transient bone marrow suppression, nausea and vomiting, pain in metastatic deposits, sialadenitis, pulmonary fibrosis, azoospermia (in males) and decreased fertility and induction of secondary solid neoplasms and leukemia (110, 111). Whole body and blood dosimetry before ^{131}I therapy for metastatic disease reduce serious complications. In general the total cumulative ^{131}I dose administered for thyroid cancer therapy during childhood and adolescence should be below 1000 mCi (112).

Prognosis

The survival of children and adolescents with PTC or FTC until 1970 was approximately 82% at 20 years (113), but in all series published since 1981 survival rates >90% have been consistently reported (114). The presence of distant metastases does not necessarily predict a poor prognosis in children, in direct contradistinction to adults with this disease. Thus, patients should not be overtreated with extensive surgery, ^{131}I or external beam irradiation.

Special considerations for patients with MTC

MTC occurs in a sporadic as well as in an autosomal dominantly inherited familial form. The familial form is further subdivided into: 1) MEN-2A, characterized by the triad of MTC, pheochromocytoma and parathyroid hyperplasia; 2) MEN-2B, featuring the sequential development of MTC and pheochromocytoma as well as the presence of marfanoid habitus and mucosal neuromas; 3) FMTC, the familial occurrence of MTC alone (79, 115). In patients with MEN 2, the C-cells of the thyroid gland undergo hyperplasia and eventual malignant transformation. MTC is particularly aggressive within the context of MEN-2B, as it becomes clinically evident during childhood [mean age of diagnosis (prior to the initiation of genetic screening): 20 years], *i.e.* 10 to 15 years earlier than in patients with MEN-2A or FMTC (116).

The gene responsible for the development of MEN-2 is the *RET* proto-oncogene (115, 117). Before *RET* was identified, testing for MEN-2 involved measurement of both baseline and iv calcium (±pentagastrin)-stimulated plasma calcitonin levels. Unfortunately, this test had several limitations, especially in the pediatric population, as normal values for baseline calcitonin and its plasma peak post-stimulation had not been established in children (94, 95). This test has been largely replaced by mutation analysis of *RET* in high-risk individuals, *i.e.* all family members of pedigrees with MEN 2 (118). *RET* mutation analysis is also recommended in all patients with MTC, as the in-

herited nature of the disorder may be missed in some apparently sporadic cases.

Once a child has been identified to have a *RET* germline mutation, prophylactic total thyroidectomy, often together with bilateral neck lymph node dissection, is recommended (116, 118). It is extremely important that the co-existence of a pheochromocytoma be excluded prior to thyroidectomy. Early total thyroidectomy is now the standard-of-care procedure for children above age 5 who harbor a *RET* germline mutation. Patients with MEN-2B usually have more aggressive cancers and, thus, total thyroidectomy with lymph node dissection may become necessary as early as during the first year of life (116, 118, 119).

Unfortunately, in many cases of MTC, the existence of local micrometastases render the permanent eradication of the disease after the first operation impossible (116). The follow-up of children and adolescents with MTC is based on the regular (every 6 to 12 months) evaluation of plasma calcitonin, a highly sensitive marker for this tumor. Additional tumor markers for the follow-up of MTC include carcino-embryonic antigen, chromogranin-A and pro-calcitonin.

Unfortunately, current imaging modalities are rarely able to localize metastatic disease, even in the face of marked hypercalcitoninemia. However, if recurrent MTC becomes anatomically definable, further (often non-curative) surgical resection of metastatic deposits is recommended. In most cases of pediatric patients with persistent MTC, the tumor grows very slowly and patients typically reach adulthood (120-122).

Finally, as is the case with all endocrinopathies, it is very important that the care of pediatric patients with any type of thyroid cancer, including MTC, be transferred to an adult endocrinologist after they reach adulthood.

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