Hyperthyroidism

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Giorgio Radetti and Federico Baronio

Hyperfunction of the thyroid gland could be related to different etiologies. The term *hyperthyroidism* refers only to a situation of hypersecretion of thyroid hormones (THs) by the thyroid gland. However, different conditions may lead to an excess of TH serum levels. This is, for example, the case of a destructive thyroiditis, where there is not a hypersecretion of TH but simply an excessive release of preformed hormones from the thyrocytes damaged by the inflammatory process. Another possibility is the exogenous intake of thyroxine for losing weight, the so-called thyrotoxicosis factitia. However, in the clinical practice ,the term *hyperthyroidism* is generically used for all such conditions. Graves' disease is the most common cause of hyperthyroidism in the pediatric age, followed by Hashimoto's thyroiditis. Other etiologies such us nodular goiter, toxic adenoma, thyroid hormone resistance syndrome, and pituitary adenoma are less frequent.

18.1 Graves' Disease (GD)

GD prevalence in the pediatric age is about 1:5,000 [1], and it is the most common cause of hyperthyroidism in children. GD incidence increases progressively with age peaking at adolescence, being 3:100,000 adolescents [2]. Females are more affected than males (F:M = 5:1).

It is a typically Th2-type autoimmune disease, resulting from a complex interaction between genetic factors, environment, and immune system. Genetic susceptibility to the disease has been linked to HLA antigens DR3, DQ 2, and DQA1*0501,

G. Radetti (✉)
Department of Paediatrics, General Hospital of Bolzano,
Via Lorenz Boehler 5, Bolzano 39018, Italy
e-mail: giorgio.radetti@gmail.com

F. Baronio
Department of Paediatrics, University of Bologna, Via Massarenti, 11, Bologna 40138, Italy
e-mail: federico.baronio@aosp.bo.it

to PTPN22 gene on chromosome 1p13, and to cytotoxic T lymphocyte antigen-4 (CTLA-4) gene on chromosome 2q33. It has been hypothesized that T- lymphocyte suppressor cells' function is diminished and their number is reduced, leading to the production of autoantibodies stimulating the thyroid function. These antibodies interact with TSH receptors in a positive functional manner by adenyl cyclase and phospholipase A2 functions, causing thyroid stimulation. Functionally, antibodies mimic TSH action, most of them having a stimulating effect and enhancing the production of thyroid hormones. However, some antibodies bind to the receptor without stimulating it. They thus block the binding of TSH to the receptor and exert an inhibitory effect. These antibodies are known as thyroid stimulation blocking antibodies. The secretion of thyroid hormones depends therefore on the balance between such opposing actions, which may contribute to explain the oscillation of thyroid hormones often seen in GD patients [1–4].

18.1.1 Clinical Aspects

Most of the GD clinical features result from the direct effect of thyroid hormones on the target tissues, but others may be a further expression of the same autoimmune process or of another associated autoimmune disease. Indeed, it is quite common to observe other autoimmune diseases such as type 1 diabetes mellitus, coeliac disease, vitiligo, etc. in GD patients.

Tachycardia is a typical sign of thyroid hormone excess on heart, but other signs such as elevated blood pressure, precordial thrill, and/or an ejection murmur due to functional insufficiency of the mitral valve may be present. There is often a delay in the diagnosis since, before coming to the attention of a pediatric endocrinologist, the child has already been assessed by other specialists, mainly a cardiologist.

Bone is also extremely sensitive to the action of thyroid hormones. Clinically, an increased growth velocity can be observed alongside an enhanced bone maturation resulting in an advanced bone age. However, it takes time for these features to develop, and therefore they can be detected in few cases, due to increased medical knowledge and care. Moreover, thyroid hormones strongly influence bone metabolism, inducing a high bone turnover with an uncoupling between the resorptive and the anabolic phase, which may result in a net bone loss and thus osteoporosis over the years. However, this mostly happens in adults suffering from an unrecognized form of subclinical hyperthyroidism, as in the case of a nodular pathology lasting for many years. In children and adolescents, where the thyrotoxic phase is generally promptly diagnosed, there is only a transitory phase of bone loss which completely recovers after normalization of thyroid hormones [5].

Muscle function may be severely compromised, mostly due to TH-induced protein wasting. A decreased muscle mass, particularly of the proximal muscles, and a reduced force can be observed. It is speculated that the toxic muscle requires more energy to function than normal, presumably because of additional ATP-consuming mechanisms. However, myasthenia gravis, another autoimmune disease. may be associated [6].

Gastrointestinal symptoms are not very common and even when present are mild. They can depend both on TH excess which causes an enhanced intestinal

transit, although not a frank diarrhea, and also on a concomitant coeliac disease. The latter should always be investigated when symptoms do not disappear following normalization of TH.

Eye involvement can be observed in most cases; however, it is not so marked as in adult patients. Signs and symptoms are milder, producing less long-term consequences. The most common sign is lid retraction, which gives a staring expression, and the lag of the lids behind the globes on downward rotation, as well as the failure to wrinkle the forehead on looking upward. All these signs are secondary to thyroid hormone excess which causes the contraction of orbicular muscles and which solves spontaneously following the normalization of TH levels. A real ophthalmopathy with inflammation of extraocular muscles, orbital fat, and connective tissue may be present in some cases, producing a proptosis together with periorbital edema and muscular dysfunction, due to inflammation of medial and lateral rectus muscles. There is now strong evidence that the immune reaction which leads to Graves' ophthalmopathy is directed against TSH receptors expressed in the orbital fibroblasts and adipocytes. The most common symptoms are due to conjunctival or corneal irritation and include burning, photophobia, tearing, pain, and a gritty or sandy sensation. It is very rare to observe a decrease in visual acuity as in adult patients. Eye drops and sunglasses are mostly used to prevent conjunctival dryness, while treatment with corticosteroids may be avoided [7, 8].

Pretibial edema is very uncommon in pediatric age. Its mechanism, similarly to ophthalmopathy, is stimulation of TSH receptors, aberrantly expressed in the skin.

A symmetrical goiter may be present, but in many cases thyroid volume is not particularly increased. A firm goiter at palpation and a thrill can be heard due to increased perfusion of the gland [9, 10].

Biochemical profile: there is usually a favorable lipid profile with low serum total and HDL cholesterol and low total cholesterol/HDL cholesterol ratio with plasma triglycerides in the lower normal range. The carbohydrate profile is characterized by an increased demand of insulin due to increased hepatic glucose production and to reduced insulin sensitivity. On the other hand, type 1 diabetes mellitus may be present. Protein metabolism is globally accelerated. Nitrogen excretion is increased, and nitrogen balance may be normal or negative, depending on whether intake meets the demands of increased catabolism or not [11].

Central and peripheral nervous system are always affected by TH excess. Already from clinical inspection, a tremor is observed, which can be associated to brisk deep tendon reflexes and eventually fasciculation of the tongue. Tremor is best observed asking the child to outstretch both hands. In general, mood swings and behavioral problems can represent a common neuropsychological complaint in hyperthyroid children [12]. Therefore, they can be referred to a child neurologist with a diagnosis of attention hyperactivity disorder, as their attention span is decreased, their sleep pattern is deteriorated, and they are hyperactive in daily life [13].

Involuntary movement disorders, such as chorea, athetosis, ballism, or truncal flexion, eventually associated to ataxia are rarely described in children affected by hyperthyroidism; symptoms remit with treatment of hyperthyroidism [14].

Autoimmune neurological conditions, such as childhood-onset demyelinating disorder [15] or disorders of neuromuscular junction [16], rarely observed as the

only symptom in children affected by GD, can represent a manifestation of the common altered immune state. As other endocrine dysfunctions, hyperthyroidism can be linked to benign intracranial hypertension in children, presenting with chronic headache, papilledema, and normal neuroimaging [17]. Correction of the endocrine alterations is associated with remission of symptoms. Finally, in children presenting with hyperthyroidism and focal neurological deficits, Moyamoya disease should be investigated [18]. Moyamoya disease is a cerebrovascular disorder characterized by bilateral stenosis or occlusion of the terminal portions of the internal carotid arteries. Typical presenting symptoms are cerebrovascular accidents and epilepsy.

Laboratory The diagnosis is very easy and is based on the detection of high levels of free thyroxine (fT4) and free thriiodothyronine (fT3) with a suppressed TSH. Confirmation for GD comes from the presence of TSH receptor antibodies (TSHR-Abs). The best approach is to show the presence of these antibodies with stimulating activity (TSI), which, however, can only be done with a functional assay able to measure the production of cyclic AMP in cultured thyroid follicular cells. This method, however, is still considered a research tool, and in most labs the presence of such antibodies is evaluated by competitive protein binding methods, which shows only the presence of antibodies competing with TSH by binding to its receptor without providing any information about whether it is a stimulating or blocking antibody. In GD, there is actually a mix of antibodies with either stimulating or inhibiting activity and the actual thyroid function results from their balance. Obviously, in a hyperthyroid state is a good suggestion for a prevailing presence of antibodies with stimulating activity. However, a change in the relative ratio might explain the fluctuation of thyroid function often observed in GD patients [11].

18.2 Hashimoto's Thyroiditis (HT)

Hashimoto's thyroiditis is the most common endocrine autoimmune disease in the pediatric age, together with type 1 insulin-dependent diabetes. Furthermore, it is almost the only form of pediatric thyroiditis since the subacute form, the painless form, and Riedel's thyroiditis are seldom seen in pediatric patients. HT is a typical, organ-specific, autoimmune disease caused by an autoimmune-mediated destruction of the thyroid gland involving apoptosis of thyroid epithelial cells. There is a diffuse lymphocytic infiltration of the thyroid, which includes predominantly thyroid-specific B and T cells, and a follicular destruction.

Independently from the actual cause, at one time point a cell-mediated autoimmune attack against the thyroid starts with lymphocytes infiltrating the thyroid. Following destruction of the thyrocytes, new antigens such as thyroid peroxidase (TPO) are released, and the immune system reacts, building new antibodies against TPO (TPOAbs). Thyroid autoantibodies are thus not causative agents but just markers of the damage of the gland. Nevertheless, TPOAbs can activate the complement and thus damage thyroid cells; however, the real role played by this antibody-dependent cell cytotoxicity is still under debate.

TSH receptor antibodies (TSHR-Abs) may also be present in the sera of patients with HT. In contrast to GD where TSHR-Abs are usually stimulatory, in HT they usually inhibit the function of the receptor and thus preferably induce hypothyroidism. However, when TSHR-Abs exert a stimulatory action, they can induce an unusually severe form of hyperthyroidism, the so-called hashitoxicosis.

18.2.1 Hyperthyroid Phase

The hyperthyroid phase is usually caused by inflammation and autonomous release of preformed, stored thyroid hormone; however, if TSHR-Abs with stimulating activity are also present, the hyperthyroid phase may be more severe, lasting several months. This situation called hashitoxicosis must be recognized since the therapeutic approach is very different. In case of simple release of preformed hormones, the treatment is just symptomatic, aimed at alleviating symptoms through the use of beta-adrenergic antagonists if tachycardia or tremulousness are present. Usually, propranolol 1–2 mg/kg divided in three to four doses is employed and titrated according to the clinical picture and the laboratory values. When, however, TSHR stimulating Abs are present, the treatment needs to be different since there is an additional source of thyroid hormones. In this case in addition to beta-adrenergic antagonists, thyreostatic drugs, as in GD, are needed.

18.3   Thyroid Nodules

Autonomous thyroid nodules may be another cause of TH excess. In adults, a multinodular goiter is a very common situation while it is rare in children and adolescents. A situation where a multinodular goiter may be relatively frequent is the McCune–Albright syndrome, caused by a postzygotic activating mutation of the alpha subunit of stimulatory G protein, which allows for a constitutive activation of the TSH receptor in absence of the ligand. Hyperthyroidism is supported by the presence of multiple hyperfunctioning nodules. Very often, there is a concomitant bone fibrous dysplasia, precocious puberty, café au lait pigmentary skin lesions, pituitary adenomas, etc.

Solitary thyroid nodule, the so-called toxic adenoma, is also a relatively rare situation in the pediatric age. Diagnosis is easily made by finding elevated TH and suppressed TSH, a palpable nodule with confirmation at ultrasound. A thyroid scintigram shows a hypercaptation in the nodule with exclusion of the remaining parenchyma. No antibodies are detected [19].

18.4   Cancer Patients

Often, children suffering from malignant diseases receive thyroid irradiation as a complement for disease treatment, following craniospinal or total body irradiation before marrow transplantation. In many cases, an actinic destructive thyroiditis may follow.

18.5   Rare Forms of Hyperthyroidism: The TSHoma and the Thyroid Hormone Resistance (RTH)

18.5.1 TSHoma

TSHoma is a pituitary adenoma, usually benign, which secretes only TSH. More often, microadenomas are observed, though hormone production is often accompanied by an unbalanced hypersecretion of the glycoprotein hormone α-subunit (α-GSU). It is a rare situation in children as compared to adults. The hormonal profile is characterized by high levels of fT3 and fT4 together with a nonsuppressed TSH. This situation cannot be clinically differentiated from the more common RTH syndrome, and thus MRI is needed. Twenty to twenty-five percent of TSHomas are mixed adenomas, characterized by concomitant hypersecretion of growth hormone or prolactin [20, 21].

18.5.2 Resistance to Thyroid Hormones (RTH)

This condition has been recognized for the first time in 1967 while the first mutations in the *THRB* gene, which code for the TSH receptor β were identified in 1989 [22]. This mutation causes a decreased tissue responsiveness to thyroid hormone (TH). It has been always though that the cause were a mutation inactivating the *THRB* gene (*RTH-β*), but lately also mutations in the *THRA* (*RTH-α*) have been detected which result in hypothyroidism. The commonest *THRB* gene mutations are heterozygous and exert a dominant negative effect on wild type receptor. Deletions on the other hand, behave as a recessive dominance since there is no negative effect on the wild type receptor. Homozygous mutations are rare and cause a very severe phenotype. Patients present with elevated fT4 and fT3 and an inappropriately normal TSH. From the clinical point of view, due to the different tissue sensitivity to TH, the patients may be perfectly normal, suffer from hypothyroidism, or be frank hyperthyroid. There may be also a discordance in sensitivity among tissues, and the patients may present with tachycardia and retarded bone age. Hyperthyroid features are predominant in those individuals being deemed to have predominant central or pituitary resistance. The diagnosis is suspected on the basis of the elevated TH together with inappropriately normal TSH; however, a TSHoma must always be excluded by imaging, and a genetic analysis should follow for confirmation. However, in a number of cases, no genetic anomalies can be detected (nonTR-RTH). Treatment is completely independent from TH serum levels and depends on the different sensitivity at tissue levels. If there are clinical signs and symptoms of hyperthyroidism, as in the pituitary form, the aim of the treatment should be lowering TH in serum. The best approach is to lower TSH secretion from the pituitary gland by the use of triiodothyroacetic acid (TRIAC), a TH analogue with low hormonal potency but high affinity to TR. Long-term experiences are promising. Another TH analogue, dextrothyroxine (d-T$_4$), had been employed but with poor results. A further possible solution is thyroidectomy alongside substitutive therapy. Up to now, there is no evidence that a prolonged period of pituitary stress (the pituitary gland continues to secret a large amount of TSH) may favor the onset of an adenoma [23].

18.6 Imaging

Up to now, thyroid scintigraphy was the most common tool for evaluation of thyroid diseases; however, currently it has been largely replaced by ultrasound evaluation, which has the advantage of identifying in real time a nodule, a lymphocyte infiltration as in the HT and in GD. Furthermore, using color Doppler function, it is possible to assess the degree of vascularization which is typically enhanced in GD (diffuse) or in secreting adenoma (focal) but not in HT. Thyroid ultrasound is so commonly employed in this field that it can be considered an integrated test in outpatient visits of a thyroidologist. Thyroid gland may be also analyzed with MRI under particular circumstances; however, use of MRI is restricted mostly to pituitary gland evaluation [24].

18.7 Fetal and Neonatal Hyperthyroidism

18.7.1 Introduction

Fetal and neonatal hyperthyroidism are rare with a prevalence of neonatal thyrotoxicosis of 1/4,000–1/50,000 pregnancies [25]; it may be a life-threatening event and could lead to death if left untreated.

18.7.2 Pathogenesis

The most frequent cause of fetal and neonatal hyperthyroidism is transplacental transfer of stimulatory TSH receptor antibody (TSHR-Abs) from a mother affected by GD [25]. The prevalence of GD in pregnancy is 0.2 % [26], and 1–12.5 % of the offspring show thyrotoxicosis at birth, and another 3 % show only biochemical signs of hyperthyroidism [25]. The prevalence of hyperthyroidism, however, increases to 22 % in the offspring of women who require treatment for GD in the third trimester of pregnancy [25]. The transplacental passage of stimulatory TSHR-Abs starts early in pregnancy, and the highest level in the fetus is reached during the third trimester, when maternal concentration of TSHR-Abs is the highest. At that time, fetal autoantibodies' levels are similar to those observed in the mother.

For this reason, the American Thyroid Association (ATA) recommends to measure TSHR-Abs during 24–28 weeks of pregnancy and to carefully look for signs of fetal thyrotoxicosis, particularly when TSHR-Abs levels are three times over normal values [27]. It must be reminded that TSHR-Abs can be detected also in women who underwent ablation of the thyroid by surgery or radioiodine as a cure for GD [25, 28, 29].

Nonautoimmune neonatal hyperthyroidism due to activating mutation of the Gsα gene or to an activating mutation of the TSH receptor gene is rare. In these cases, severe permanent fetal and neonatal hyperthyroidism is due to molecular abnormalities of the TSH receptor that lead to its permanent activation. Hyperthyroidism control is generally difficult to achieve, and most patients undergo total thyroidectomy [30]. Rare cases of transient hyperthyroidism related to hydatiform mole and thyrotropin receptor hypersensitive to human chorionic gonadotropin have been reported [31].

18.7.3 Diagnosis of Fetal Hyperthyroidism

At the beginning of pregnancy, determination of TSHR-Abs should be performed in all pregnant women with GD and in euthyroid pregnant women with a history of GD who underwent thyroidectomy. If TSHR-Abs are present, the fetus should be carefully monitored because of the risk to develop thyrotoxicosis [32].

The characteristic clinical features of fetal hyperthyroidism are intrauterine growth retardation [33], nonimmune fetal hydrops, craniosynostosis, tachycardia, and fetal goiter.

Fetal tachycardia related to thyrotoxicosis is very common but not always present [34] and is characterized by a consistent resting fetal heart rate above 160 beats/min measured by Doppler ultrasonography.

The development of goiter in utero, however, might also be related to the overtreatment of the mother with antithyroid drugs; in these cases, goiter usually shrinks following a reduction or discontinuation of the administered drugs.

In selected cases, the confirmation of fetal hyperthyroidism relies on the direct assessment of serum fetal TH by cordocentesis. This procedure, however, may lead to severe complications for the fetus (infection, bradycardia, hemorrhage, death) and should be performed by experienced doctors and only if absolutely necessary [34]. Usually, this approach is needed in doubtful cases, for instance, when a mother with GD is being treated with antithyroid drugs and/or if she underwent ablation of the thyroid [35].

18.7.4 Prognosis of Fetal Hyperthyroidism

Fetal hyperthyroidism could be extremely harmful with an overall mortality of 12–20 % due to heart failure. In untreated women with GD during pregnancy, preterm delivery occurs in 53 % and intrauterine fetal death in 24 % of cases. In treated pregnancies, preterm delivery can occur in 4–11 % of cases and intrauterine death in 5–7 %.

18.7.5 Diagnosis of Neonatal Hyperthyroidism

In neonates, the clinical features of thyrotoxicosis are low birth weight for gestational age, premature birth, microcephaly, frontal bossing and triangular facies, diffuse goiter, warm and moist skin, irritability, hyperactivity, restlessness and poor sleep, stare and occasionally exophthalmos, diarrhea, poor weight gain with good appetite, vomiting, cardiac failure and arrhythmias, systemic and pulmonary hypertension, hepatosplenomegaly, jaundice, hyperviscosity syndrome, thrombocytopenia, and craniosynostosis [35]. Among the other signs, persistent acrocyanosis, hepatosplenomegaly, lymphadenopathy, and thymic enlargement are also reported. Bone age is generally advanced [25].

The diagnosis should be suspected in neonates born to mothers affected by GD who have been treated with antithyroid drugs during the third trimester of pregnancy and excluded in those who underwent ablation of the thyroid for GD [25, 28, 29].

Most cases of neonatal GD are suspected because of the maternal history, but in rare cases they are diagnosed also by neonatal screening [36].

In suspicious cases, serum fT4 and TSH should be measured at delivery or soon thereafter. It must be reminded that the concomitant transplacental passage of antithyroid drugs usually delays the onset of the clinical picture of hyperthyroidism till 10–20 days of life [37].

18.7.6 Prognosis of Neonatal Hyperthyroidism

Neonatal GD is generally a transient disorder, limited by the clearance of maternal antibody from the baby's circulation, and the symptoms of thyrotoxicosis usually disappear after 3–12 weeks from delivery [38]. It could be, however, life threatening, with detrimental effects on heart and central nervous system development. The degree of cardiac involvement determines the short-term prognosis, while the long-term effects of hyperthyroidism involve neurological development [38, 39].

Neonates with thyrotoxicosis improve rapidly with treatment; however, a reduced IQ in some of these patients, even if adequately treated, has been described, supporting the adverse effect of thyrotoxicosis on developing central nervous system. Moreover, growth retardation, craniosynostosis, hyperactivity, and developmental or behavioral problems have been reported as long-term sequelae of neonatal hyperthyroidism, but their correlation with the adequacy of treatment still remains unclear [40].

Finally, the presence of central hypothyroidism has also been reported in neonates born to mothers with GD, attributable to in utero exposure of hypothalamus and pituitary glands to high TH levels. It has been suggested that this is the consequence of an inadequate maternal treatment during pregnancy [41].

18.8 Treatment of Hyperthyroidism

18.8.1 Fetal Hyperthyroidism

Fetal thyrotoxicosis should be treated by administering antithyroid drugs like methimazole (MMI), propylthiouracil (PTU), and carbimazole to the mother [42]. A useful hint for treatment monitoring is the observation that there is a good correlation between maternal and fetal fT4 levels. On the other hand, overtreatment should be avoided, since treating pregnant women with antithyroid drugs in a dosage which lowers the maternal fT4 levels into normal range may lead to fetal hypothyroidism, which should always be suspected when goiter size increases and

bradycardia ensues. Prompt reduction of antithyroid treatment to the mother restores euthyroidism and reduces goiter while rarely intramniotic injections of thyroxin are needed [43].

Altogether, it is commonly suggested to adjust the antithyroid drug treatment in order to keep maternal fT4 in the upper normal to mildly thyrotoxic range [44]. Treatment is usually started with PTU (in the first trimester of pregnancy) at 100–200 mg daily or MMI 10–20 mg daily, and after 1 month the dose should be adjusted to maintain fT4 in the upper one-third of each trimester-specific reference interval [45]. Serum TSH levels of 0.1–2.0 mU/l are appropriate, but TSH <0.1 mU/l is also acceptable if a patient is in good health conditions and fT4 is adequate. Classically, PTU is the drug of choice during the first trimester of pregnancy because the use of MMI has been more often associated to the occurrence of aplasia cutis and other malformations (tracheoesophageal fistula and embryopathy) [46]. In particular, it seems of crucial importance to avoid exposure of the fetus to MMI during gestational weeks 6–10, which is the period of major organogenesis.

Monitoring fT4 levels in the mother, fetal thyroid dimension (monthly thyroid ultrasound to detect goiter onset), fetal growth, and heart rate is mandatory during antithyroid treatment.

18.8.2 Neonatal Hyperthyroidism

Treatment of neonatal thyrotoxicosis is based on antithyroid drugs (MMI, PTU), beta-adrenergic receptor blocking agents (propranolol, atenolol), iodine (lugol solution, SSKI), or iodinated contrast agents and, when needed, glucocorticoids and digoxin. MMI should be administered at a dosage of 0.25–1.0 mg/kg per day every 8 h. PTU is also effective, but it has more frequent and severe side effects, including a risk of hepatotoxicity [47], and for these reasons several scientific associations do not recommend PTU as a first-line treatment for GD in children [48].

Propranolol (2 mg/kg per day every 8 h) should be started to control neuromuscular and cardiovascular hyperactivity while atenolol (1 mg/kg daily, one single daily dose) could be preferred for a more cardio-specific blockage.

Lugol's solution (126 mg iodine/mL) should be administered as one drop (8 mg) orally every 8 h and SSKI (saturated solution of potassium iodide – 1 g/ml) as one to two drops daily, to reduce thyroid hormones release.

Glucocorticoids (prednisolone 2 mg/kg/day) inhibit thyroid hormone secretion and decrease peripheral conversion of T4 to triiodothyronine (T3) and may be helpful in extremely ill infants.

Digoxin could be administered in children with heart failure.

As the clinical and biochemical picture of thyrotoxicosis improves, treatment should be gradually reduced and then discontinued. The treatment may require several adjustments, with the thyroid function being monitored frequently (weekly). Generally, medical treatment would be withdrawn within 12 weeks although it can be continued for 6 months or even longer.

18.8.3 Hyperthyroidism in Childhood and Adolescence

The common treatment options for GD in children include antithyroid drugs (ATDs), subtotal or near-total thyroidectomy, and radioactive iodine (RAI) – I131; however, there is no general consensus on the optimal treatment.

It is common practice to start treatment with ATD; however, this approach may be associated to poor compliance with high relapsing rate or be complicated by toxicity. In case of relapses or drug toxicity, second-line options that are considered radical treatment are advisable and consist in total (or near-total) surgical removal of the thyroid gland or its destruction with radioimmune iodine (I 131).

ß blockers (except in patients with asthma or cardiac failure) could be associated during the first 2 weeks of management to relief tachycardia [49].

18.8.3.1 ATD Therapy

Carbimazole, its active metabolite, methimazole (MMI), and propylthiouracil (PTU) are the antithyroid drugs commonly used in children and adolescents as first-line treatment of GD.

In less than 25 % of cases, patients treated with ATD may show minor side effects (urticaria, rash, gastrointestinal problems, arthralgia). Major side effects such as agranulocytosis, drug-induced hepatitis, and production of cytoplasmic antineutrophil antibodies may be seen, even if with really low incidence. Antibody-positive vasculitis occurs only in exceptional cases.

Side effects of ATD may be dose related and usually occur within the first 6 months in 90 % of patients. MMI has a longer half-life and is effective when given as a single daily dose. MMI dose <10 mg/day is considered safe.

MMI (or carbimazole) starting dose is 0.5–1 mg/kg/day, with a maximum dose of 30 mg per day. After 2–4 weeks, as thyroid function normalizes, the dose should be reduced gradually by 30–50 %. The goal of ATD treatment is to restore normal thyroid function rather than reduce autoimmunity. However, it has been shown that euthyroidism has a beneficial effect on TSHR-Abs production and remission of GD [50]. Currently, there is no evidence of major efficacy of a combination of L-T4 (15) and ATD.

Remission is achieved after 24 months of ATD treatment by <30 % of children [51–54]. More prolonged use of ATD should be planned (2–4 years) in uncured cases.

In patients who do not undergo remission during ATD, the choice of the optimal therapeutical option still shows some uncertainties, as there are no prospective studies on effective long-term efficacy and safety of prolonged use of ATD, and ablative treatments such as surgery or RAI are followed by permanent hypothyroidism [49].

18.8.3.2 Surgical Treatment

Thyroid surgery is generally recommended as radical treatment choice in those hyperthyroid children and adolescents with larger thyroid goiter or with ophthalmopathy.

Nowadays, total (or near-total) thyroidectomy is preferred to subtotal (or partial) thyroidectomy [1]. For 1 week before surgery, five to ten drops of lugol solution

should be administered to reduce thyroid gland vascularity. Thyroidectomy-related risks such as hypoparathyroidism, vocal cord palsy due to recurrent laryngeal nerve injury, and keloid formation have relatively low incidence (15 % of cases) in experienced pediatric surgery centers [55].

18.8.3.3 Radioactive Iodine Treatment (RAI)

In children with hyperthyroidism, RAI is an effective treatment at large doses of I131 (220–275 μCi/g, corresponding to about 250 Gy) [56].

Secondary hypothyroidism that in almost all cases follows RAI treatment should be promptly treated with adequate lifelong levothyroxine therapy. Further prospective long-term studies of potential side effects (like thyroid malignancy, hyperparathyroidism) of this treatment are needed.

18.9   Long-Term Outcome

As mentioned above, less than 30 % of children show remission from GD after 2 years from a first course of ATD (average treatment period of 2 years). About 75 % of patients relapse within 6 months of the end of drug treatment, whereas only 10 % relapse after 18 months.

Due to the lack of prospective studies in children, it is difficult to predict who will relapse and would be better if undergoing early radical treatment. Previous studies take in consideration as predictive markers age, goiter size, severity of hyperthyroidism at the onset, TSHR-Abs levels, and duration of ATD.

A recent study from Leger et al. showed in GD children a positive correlation between the risk of relapses and young age, non-Caucasian origin, and high serum fT4 and TSHR-Abs levels at the onset [57]. Furthermore, the authors showed an inverse correlation between the risk of relapses and duration of ATD, emphasizing that long-term treatment reduces the risk of disease recurrence.

References

1. Brix TH, Kyvik KO, Hegedus L (1998) What is the evidence of genetic factors in the etiology of Graves' disease? A brief review. Thyroid 8(8):727–734
2. Brix TH, Kyvik KO, Christensen K et al (2001) Evidence for a major role of heredity in Graves' disease: a population-based study of two Danish twin cohorts. J Clin Endocrinol Metab 86(2):930–934
3. Brand OJ, Gough SC (2010) Genetics of thyroid autoimmunity and the role of the TSHR. Mol Cell Endocrinol 322:135–143
4. Saitoh O, Nagayama Y (2006) Regulation of Graves' hyperthyroidism with naturally occurring CD4+CD25+ regulatory T cells in a mouse model. Endocrinology 147:2417–2422
5. Lucidarme N, Ruiz JC, Czernichow P et al (2000) Reduced bone mineral density at diagnosis and bone mineral recovery during treatment in children with Graves' disease. J Pediatr 137:56–62
6. Zürcher RM, Horber FF, Grünig BE et al (1989) Effect of thyroid dysfunction on thigh muscle efficiency. J Clin Endocrinol Metab 69:1082–1086

7. Goldstein SM, Katowitz WR, Moshang T et al (2008) Pediatric thyroid-associated orbitopathy: the Children's hospital of Philadelphia experience and literature review. Thyroid 18:997–999

8. Gogakos AI, Boboridis K, Krassas GE (2010) Pediatric aspects in Graves' orbitopathy. Pediatr Endocrinol Rev 7:234–244

9. Birrell G, Cheetham T (2004) Juvenile thyrotoxicosis; can we do better? Arch Dis Child 89:745–750

10. Leblicq C, Duval M, Carmant L et al (2013) Rising serum thyroxin levels and chorea in Graves' disease. Pediatrics 131:e616–e619

11. Bahn Chair RS, Burch HB, Cooper DS et al (2011) Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. Thyroid 21:593–646, Erratum in: Thyroid. 2011, 21(10):1169. Thyroid. 2012, 22(11):1195

12. Loomba-Albrecht LA, Bremer AA, Styne DM et al (2011) High frequency of cardiac and behavioral complaints as presenting symptoms of hyperthyroidism in children. J Pediatr Endocrinol Metab 24:209–213

13. Sims EK, Eugster EA, Nebesio TD (2012) Detours on the road to diagnosis of Grave's disease. Clin Pediatr (Phila) 51(2):160–164

14. Seeherunvong T, Diamantopoulos S, Berkovitz GD (2007) A nine year old girl with thyrotoxicosis, ataxia, and chorea. Brain Dev 29:660–661

15. Mitchell RS, Yager JY, Marks SD (2007) Childhood onset demyelination and Graves' disease: shared antigen or autoimmune clustering? J Pediatr Endocrinol Metab 20(11):1233–1236

16. Perlman SJ, Zaidman CM (2013) Childhood Grave's disease masquerading as myasthenia gravis. J Child Neurol 28:1309–1311

17. Merkenschlager A, Ehrt O, Müller-Felber W et al (2008) Reversible benign intracranial hypertension in a child with hyperthyroidism. J Pediatr Endocrinol Metab 21:1099–1101

18. Sasaki T, Nogawa S, Amano T (2006) Co-morbidity of moyamoya disease with Graves' disease. Report of three cases and a review of the literature. Intern Med 45:649–653

19. Williams JL, Paul D 3rd, Bisset G (2013) Thyroid disease in children: part 2: state-of-the-art imaging in pediatric hyperthyroidism. Pediatr Radiol 43:1254–1264

20. Nakayama Y, Jinguji S, Kumakura S (2012) Thyroid-stimulating hormone (thyrotropin)-secretion pituitary adenoma in an 8-year-old boy: case report. Pituitary 15:110–115

21. Rabbiosi S, Peroni E, Tronconi GM et al (2012) Asymptomatic thyrotropin-secreting pituitary macroadenoma in a 13-year-old girl: successful first-line treatment with somatostatin analogs. Thyroid 22:1076–1079

22. Refetoff S (1994) Resistance to thyroid hormone: an historical overview. Thyroid 4:345–349

23. Pohlenz J, Weiss RE, Macchia PE et al (1999) Five new families with resistance to thyroid hormone not caused by mutations in the thyroid hormone receptor beta gene. J Clin Endocrinol Metab 84:3919–3928

24. Williams JL, Paul D, Bisset G 3rd. (2013) Thyroid disease in children: part 2: state-of-the-art imaging in pediatric hyperthyroidism. Pediatr Radiol 43:1254–64

25. Ogilvy-Stuart AL (2002) Neonatal thyroid disorders. Arch Dis Child Fetal Neonatal Ed 87:F165–F171

26. Glinoer D (1997) The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. Endocr Rev 18:404–433

27. Barbesino G, Tomer Y (2013) Clinical review: clinical utility of TSH receptor antibodies. J Clin Endocrinol Metab 98:2247–2255

28. Mitsuda N, Tamaki H, Amino N et al (1992) Risk factors for developmental disorders. Obstet Gynecol 80:359–364

29. Polak M (2011) Thyroid disorders during pregnancy: impact on the fetus. Horm Res Paediatr 76:97–101

30. Kopp P, van Sande J, Parma J et al (1995) Brief report: congenital hyperthyroidism caused by a mutation in the thyrotropin-receptor gene. N Engl J Med 332:150–154

31. Rodien P, Brémont C, Sanson ML et al (1998) Familial gestational hyperthyroidism caused by a mutant thyrotropin receptor hypersensitive to human chorionic gonadotropin. N Engl J Med 339:1823–1826

32. Polak M, Le Gac I, Vuillard E et al (2004) Fetal and neonatal thyroid function in relation to maternal Graves' disease. Best Pract Res Clin Endocrinol Metab 18:289–302

33. Farrehi C (1968) Accelerated maturity in fetal thyrotoxicosis. Clin Pediatr 7:134

34. Chan GW, Mandel SJ (2007) Therapy insight: management of Graves' disease during pregnancy. Nat Clin Pract Endocrinol Metab 3:470–478

35. Polak M, Legac I, Vuillard E et al (2006) Congenital hyperthyroidism: the fetus as a patient. Horm Res 65:235–242

36. Tajima T, Jo W, Fujikura K et al (2009) Elevated free thyroxin levels detected by a neonatal screening system. Pediatr Res 66:312

37. Weber G, Ielo V, Vigone MC et al (2001) Neonatal hyperthyroidism: report of eight cases. Ital J Pediatr 27:757

38. Léger J, Carel JC (2013) Hyperthyroidism in childhood: causes, when and how to treat. J Clin Res Pediatr Endocrinol 5 Suppl 1:50–6

39. Radetti G, Zavallone A, Gentili L, Beck-Peccoz P, Bona G (2002) Foetal and neonatal thyroid disorders. Minerva Pediatr 54:383–400

40. Daneman D, Howard NJ (1980) Neonatal thyrotoxicosis: intellectual impairment and craniosynostosis in later years. J Pediatr 97:257

41. Kempers MJ, van Tijn DA, van Trotsenburg AS et al (2003) Central congenital hypothyroidism due to gestational hyperthyroidism: detection where prevention failed. J Clin Endocrinol Metab 88:5851

42. Azizi F (2006) The safety and efficacy of antithyroid drugs. Expert Opin Drug Saf 5:107–116

43. Miyata I, Abe-Gotyo N, Tajima A et al (2007) Successful intrauterine therapy for fetal goitrous hypothyroidism during late gestation. Endocr J 54:813

44. Luton D, Le Gac I, Vuillard E et al (2005) Management of Graves' disease during pregnancy: the key role of foetal thyroid gland monitoring. J Clin Endocrinol Metab 90:6093–6098

45. Momotani N, Noh J, Oyanagi H et al (1986) Antithyroid drug therapy for Graves' disease during pregnancy. Optimal regimen for fetal thyroid status. N Engl J Med 315:24–28

46. Foulds N, Walpole I, Elmslie F et al (2005) Carbimazole embryopathy: an emerging phenotype. Am J Med Genet 132:130–135

47. Rivkees SA, Szarfman A (2010) Dissimilar hepatotoxicity profiles of propylthiouracil and methimazole in children. J Clin Endocrinol Metab 95:3260

48. Bahn RS, Burch HS, Cooper DS et al (2009) The role of propylthiouracil in the management of Graves' disease in adults: report of a meeting jointly sponsored by the American Thyroid Association and The Food and Drug Administration. Thyroid 16:673

49. Léger J, Kaguelidou F, Alberti C et al (2014) Graves' disease in children. Best Pract Res Clin Endocrinol Metab 28:233–243

50. Kaguelidou F, Alberti C, Castanet M et al (2008) Predictors of autoimmune hyperthyroidism relapse in children after discontinuation of antithyroid drug treatment. J Clin Endocrinol Metab 93:3817–3826

51. Lee JA, Grumbach MM, Clark OH (2007) The optimal treatment for pediatric Graves' disease is surgery. J Clin Endocrinol Metab 3:801–803

52. Kaguelidou F, Carel JC, Leger J (2009) Graves' disease in childhood: advances in management with antithyroid drug therapy. Horm Res 71:310–317

53. Rivkees SA (2010) Pediatric Graves' disease: controversies in management. Horm Res Paediatr 74:305–311

54. Schenk D, Donaldson M, Cheetham T (2012) Which antithyroid drug regimen in paediatric Graves' disease? Clin Endocrinol (Oxf) 77:806–807

55. Sosa JA, Tuggle CT, Wang TS et al (2008) Clinical and economic outcomes of thyroid and parathyroid surgery in children. J Clin Endocrinol Metab 93:3058–3065

56. Bahn RS, Burch HB, Cooper DS et al (2011) Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. Endocr Pract 17:456–520

57. Leger J, Gelwane G, Kaguelidou F et al (2012) Positive impact of long-term antithyroid drug treatment on the outcome of children with Graves' disease: national long-term cohort study. J Clin Endocrinol Metab 97:110–119