Chapter

Hyperthyroidism in Children

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Abstract

Hyperthyroidism is the state of excessive synthesis and release of the thyroid hormones by thyrocytes. Graves' Disease is the most common cause of hyperthyroidism in children. The condition may occur at any age but the prevalence increases with age. According to the classical paradigm, coexistence of genetic susceptibility, environment triggers and immunological dysfunction are responsible for its development. Diagnosis of Graves' Disease is based on presence of characteristic clinical symptoms, TSH receptor antibodies and excess of thyroid hormones. The management in pediatric population involves mainly pharmacotherapy (thyrostatics, β-adrenolitics), in resistant cases radical radioiodine I^{131} therapy or surgical treatment is necessary.

Keywords: hyperthyroidism, Graves' Disease, children, autoantibodies, antithyroid drugs

1. Introduction

Hyperthyroidism (hyperthyreosis) is the condition that occurs due to excessive synthesis and release of the thyroid hormones T_3 (triiodothyronine) and/or T_4 (thyroxine) by thyrocytes and as a result of hyperstimulation of cells having receptors specific to these hormones.

A negative feedback blocks the secretion of thyrotropin (TSH) from the pituitary gland. Subclinical hyperthyroidism is characterized by normal levels of free thyroxine (fT_4) and free triiodothyronine (fT_3), with TSH below the reference range in the blood.

The term "thyrotoxicosis" refers to the clinical syndrome associated with the increased level of thyroid hormones caused by their enhanced production by the thyroid gland, their excessive release resulting from the gland destruction (e.g. the Hashitoxicosis phase in chronic thyroidits of Hashimoto's type), as well as due to the exogenous supply of thyroid hormone preparations in an abnormal, too large dose, and casual poisoning with thyroid hormone preparations (thyrotoxicosis factitia). Thus, thyreotoxicosis refers not only to the level of hormones in the blood, but is also associated with the level of sensitive cells that undergo activation, which leads to the manifestation of subjective and objective symptoms.

2. Causes of hyperthyroidism in children

The causes of hyperthyroidism in children include:

- Graves' Disease (toxic diffuse goiter, struma diffusa toxica) accounting for 95–99% of hyperthyroidism cases in children and approximately 60% in adults.

- toxic nodular goiter (Plummer's disease) being much less common in children than in adults; most frequently occurring as a single nodule, especially in older children.
- the Marine-Lenhart's syndrome, in which an overactive thyroid nodule co-occurs with Graves' Disease in the same patient.
- thyroiditis.
- the initial stage of Hashimoto's disease.
- phase 1 subacute (viral) thyroiditis.
- poisoning with thyroid hormones – iatrogenic hyperthyroidism.
- Iodine Basedow Syndrome – hyperthyroidism develops due to the application of inorganic iodides, which act as triggering factors that induce hyperthyroidism on the grounds of autoimmunization.
- amiodarone-induced thyrotoxicosis (amiodarone has a chemical structure resembling that of thyroxine, one tablet contains approximately 75 mg of iodine!)
- hyperthyroidism in the course of follicular and papillary cancers.
- McCune-Albright syndrome is associated with the point mutation of the gene encoding the alpha subunit of the Gs protein, resulting in permanent activation of adenylyl cyclase; its main components are: fibrous dysplasia, café au lait spots, overactivity of many endocrine glands.
- the so called early effect of radioiodine I^{131} treatment for the thyroid.
- ovarian goiter (struma ovarii) - a substantial amount of thyroid tissue in ovarian tumour.
- thyrotropic pituitary adenomas – secondary hyperthyroidism (elevated values of TSH and thyroid hormones).
- pituitary thyroid hormone resistance – elevated levels of TSH and thyroid hormones.
- false hyperthyreosis in patients taking biotin preparations – in some cases even TSH receptor antibodies appear [1, 2].

3. Etiology and etiopathogenesis of Graves' Disease

The disease is named after an Irish physician, Robert Graves, who was the first to describe the symptoms of hyperthyrosis. In non-English speaking countries, the two-word term is commonly used as the name of a German doctor, Karl Adolph von Basedow, is added. This is an autoimmune disease, in which stimulating antibodies activate TSH receptor, leading to the thyroid growth as well as to unrestrained production and release of thyroid hormones.

Last decades have shown a constant increase in the incidence of autoimmune thyroid diseases (AITD). It is estimated that the problem affects approximately 5% of the world population. However, Graves' Disease is rarely diagnosed in the pediatric population. Its prevalence accounts for about 0.02% and children constitute less than 5% of all the patients. Nevertheless, it is Graves' Disease that remains the most common cause of hyperthyreosis in children, being responsible for 10–15% of all thyroid disorders in this group. Among pediatric patients, Graves' Disease may occur at any age but the morbidity rate increases with age, having its peak in adolescence. Its annual incidence among younger patients is 0.1 per 100,000 as compared to 3.0 per 100,000 at puberty. In the USA, Graves' Disease affects 0.2–0.4% of children and adolescents, i.e. 1 per 10,000, whereas in Hongkong it is diagnosed in 14 children per 100,000 a year. Sex distribution in the age group of up to 11 years is comparable, but in the older age group, girls are more frequently affected than boys (6–8,1).

It is estimated based on the research into monozygotic twins that the etiology of AITD has genetic causes in approximately 80% of cases, as compared to 20% due to environmental factors. Hashimoto thyroiditis and Graves' Disease share some of the genes.

Genes likely to be responsible for the development of AITD can be divided into two groups:

1. genes modulating the immune system, i.e. *HLA-DR*, *CD40*, CTLA-4, PTPN22, CD25, *FoxP3.*

2. genes specific to the thryroid gland: the gene for thyroglobulin (Tg) and the TSH receptor (TSHR) gene.

Additional genes may also play a role, being involved in the differentiation of AITD phenotypes, disease severity and response to the therapy.

Genes whose mutations may be responsible for the disease onset include:

- *GD-1* (chromosome 14q31).

- *GD-2* (chromosome 20q11.2).

- *GD-3* (chromosome Xq21).

- *HLA-DR3* gene described mainly as the main gene in the development of Graves' Disease. The presence of arginine at position 74 of the HLA-DRβ chain predisposes to AITD disclosure, whereas glutamine at the same position shows protective functions.

- *CD40* performs a key function in the interaction between antigen-presenting cells and T lymphocytes. CD40, found on B cells, ensures normal signal for proliferation, differentiation and production of IgG. Therefore, the CD40 gene predisposes to the development of Graves' Disease, which is to a large extent B-cell dependent.

- *CTLA-4* is present on the surface of T cells and inhibits their excessive response to the antigen. Moreover, it shows the expression on regulatory T cells, thus playing a major role in promoting their suppresive functions.

- CD25 gene polymorphism inhibits Treg functions, thus promoting autoimmunity. A latest study has described the level of mRNA expression for the

genes encoding T-bet and GATA3, main regulators of Th1 and Th2 differentiation, respectively, and for the cytokines secreted by (IFNγ) and Th2 (IL4) in patients with Graves' Disease. The levels of the expression of mRNA T-bet and IFNγ are substantially elevated in patients, whereas those of GATA3 and IL4 remain decreased.

Also mutations of the gene encoding the expression of thyroglobulin, located on chromosome 8 and the autoimmune regulator gene located on chromosome 21 predispose to Graves' Disease. Moreover, vulnerability to develop ophthalmopathy in the course of Graves' Disease has been studied, with the involvement of CTLA-4 genes, tumor necrosis factor α (TNFα), adhesion molecule 1 (ICAM-1), interferon γ (IFN-γ), insulin-like growth factor 1 receptor (IGF-1R), protein inhibiting the pathway of signal 3 transduction (SOCS3), thyroid peroxidase (TPO) and calsequestrin 1 (CASQ1) [3–5].

The environmental factors that trigger the cascade leading to AITD include:

- infections, both viral and bacterial, may be responsible for the loss of tolerance and development of AITD; in the etiology of Graves' Disease *Yersinia enterocolitica* is the best known pathogen having specific bindings to TSH, recognized by antibodies against TSH receptor; *Y. enterocolitica* ompF (outer membrane porin F) produces antibodies and according to some sources is responsible for the process of molecular mimicry;

- stress -stress hormones (glycocorticosteroids, catecholamines) may induce the production of IL4, IL6, IL12 by dendritic cells, stimulate Th2, Th17 or Th1 cells and lead to Treg cell apoptosis, which promotes the pathogenesis of Graves' Disease;

- radiation -radioiodine treatment for toxic nodular goiter may contribute to the development of Graves' Disease or ophthalmopathy; the effect of radiotherapy on thyroid function depends on a number of factors, such as age, sex, the presence of antithyroid antibodies, iodine intake, etc.;

- exposure to tobacco smoke -according to the available data the proportion of smokers is elevated in patients with orbitopathy (64.2%) and Graves' Disease (47.9%) as compared to the control group (30%); smoking increases the risk of Graves' Disease twice and orbitopathy 3–4 times; moreover, the risk is associated with treatment failure and severity of ophthalmopathy;

- excessive iodine supply -iodine-induced hyperthyrosis, also called iodine-Basedow syndrome, refers particularly to patients with nodular goiter or to a population in which salt iodination program has been recently implemented;

- medications -interferon-α, alemtuzumab, highly active antiretroviral drugs capable of AITD induction; a classic example of the hyperthyreosis-inducing drug is amiodarone, a benzuforan derivative rich in iodine, whose structure resembles that of thyroid hormones; there are two types of amiodarone-induced thyrotoxicosis (AIT):

    - I -caused by enhanced production of thyroid hormones,

    - II - manifested by inflammation and destruction of thyrocytes.

- vitamin D_3 deficiency.
- contaminations [6–9].

However, Graves' Disease can be associated with the involvement of a combination of factors. The disease may even appear a long time after contact with a stimulus. Immunologically, the pathogenesis of Hashimoto thyroiditis is based on the predominance of cellular response, whereas the pathogenesis of Graves' Disease is associated with humoral response. This is, however, a gross simplification, as these processes overlap. Up to now, it has been thought that hyperstimulated $CD4^+$ T cells play a major role in the pathogenesis of Hashimoto thyroiditis. T helper 1 cells (Th1) produce interferon γ. Anti-TSHR antibodies against TSH receptor, whose differentiation is induced by Th1 cells, belong mainly to the IgG1 subgroup. Th1 cells can also stimulate the production of antibodies by IL10 secretion, which in turn stimulates B cells. Helper T2 cells (Th2) secrete interleukin 4 (IL4) and lead to the stimulation and production of B cells and plasmatic cells, which produce IgG4 antibodies against thyroid-attacking antigens (**Figure 1**).

Th17 cells originate from Th under the effect of various factors, i.e. TGFB, IL6, IL21, IL23 or STAT3. They produce interleukin 17 (IL17), involved in the promotion of inflammatory processes. Th17 cells show the expression of CCR6, IL23R, IL12Rβ2 and CD161. Their large population has been found in patients with AITD. In turn, Tregs make up an opposite population of lymphocytes that are mainly involved in the inhibition of immune hyperreaction; hence, their function is impaired or their number is decreased in various autoimmune diseases, including AITD. The analysis of the Th17/Treg proportion in children showed a reduced number of phenotypes characteristic of Treg cells: $CD4^+IL17^+/CD4^+CD25^+CD127^-$ and $CD4^+IL17^+/CD4^+CD25^+CD127^-FoxP3^+$ in patients with Graves' Disease as compared to the control group.

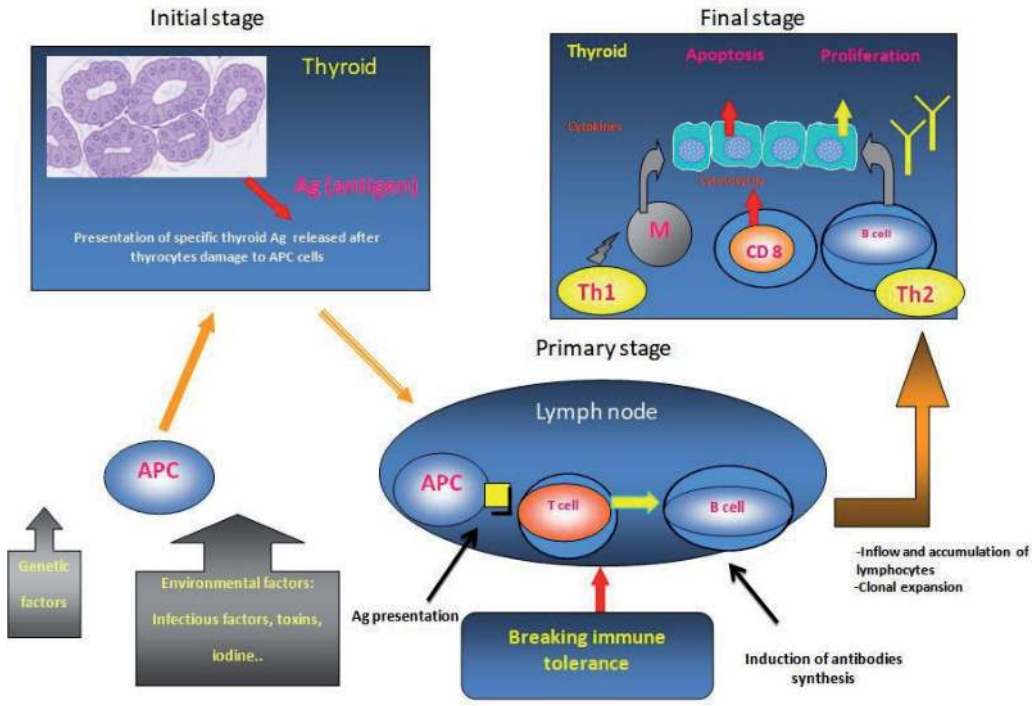

Figure 1.
Model of Graves' Diseases etiopathogenesis; APC – antigen presenting cell; M – macrophages, CD8 – cytotoxic cells; cells – Th1, th2.

Inflammation is an orderly process that should result in the elimination of a pathogenic factor and recovery of physiological condition, thus reflecting an effective immune response. One of the major traits of inflammatory condition is its self-limiting nature. The impaired suppresive function of lymphocytes leads ultimately to uncontrolled tissue injury and chronic inflammation. In the last few years, the maintenance of immunological tolerance has been ascribed to the subpopulation of B cells called B regulatory cells (Bregs). Their role has been emphasized in many autoimmune diseases which show both abnormal count and disturbed functionality of Bregs. Throughout the decades the knowledge of Bregs was based mainly on the research conducted on mice. The breakthrough was a study by Janeway et al., who in mice deprived of B cells observed a failure to recover after previous experimental autoimmune encephalomyelitis (EAE). Moreover, interleukin 10 (IL10) was found to be responsible for regulatory properties. Immature and mature B cells and plasmoblasts are thought to have a potential to differentiate towards Bregs producing IL10 both in mice and people. There is a strong potentiation of the function between Bregs and Tregs. On the other hand, Bregs inhibit differentiation of Th1 and Th17 cells by suppressing the production of proinflammatory cytokines as well as proliferation of dendritic cells (**Figure 2**).

Apart from IL10 secretion, Bregs are characterized by the production of other factors, i.e. transforming growth factor β (TGFβ) and interleukin 35 (IL35) (**Figure 3**). Through the production of TGF-β, Bregs activated by lipopolysaccharide (LPS) are able to induce the apoptosis of effector $CD4^+$ T cells and inactivity of $CD8^+$ T cells. Another mechanism inhibiting the immune response is due to the effect of IL35 which may inhibit the effector function of T cells; it also induces Bregs, promotes differentiation of B cells to Bregs secreting not only IL35, but also IL10.

Authors still pose a question whether Bregs constitute a separate cell line, in which a specific factor controls the expression of the genes responsible for their suppresive function or appear in response to the action of specific factors that stimulate B cells in a suitable environment. Immature and mature B cells and plasmoblasts and plasmatic cells may act as Bregs. Also B10 cells may differentiate into cells producing antibodies following termination of IL-10 production. In response to the inflammatory process, the level of Bregs increases and they gain the ability to regulate immunity. Thanks to the combination of antigen with B cell receptor (BCR), Bregs detect the inflammatory signal and induce regulatory effects [10–14].

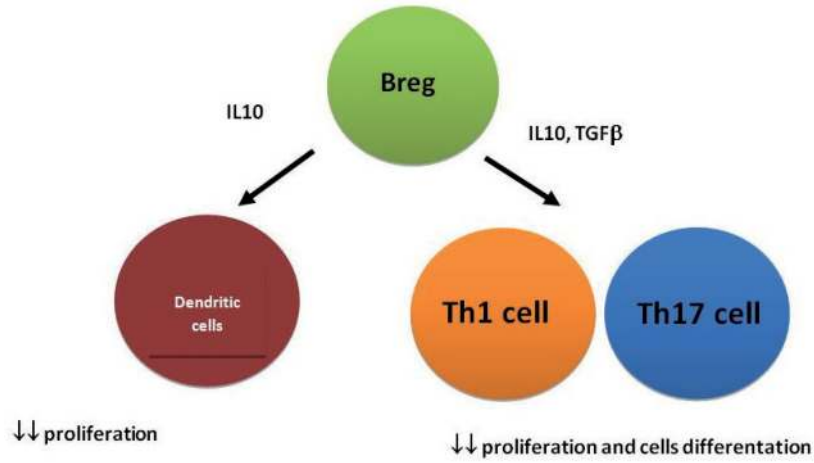

Figure 2.
Role of B regulatory cells in inhibiting differentiation of lymphocytes Th1 and Th17 and dendritic cells proliferation.

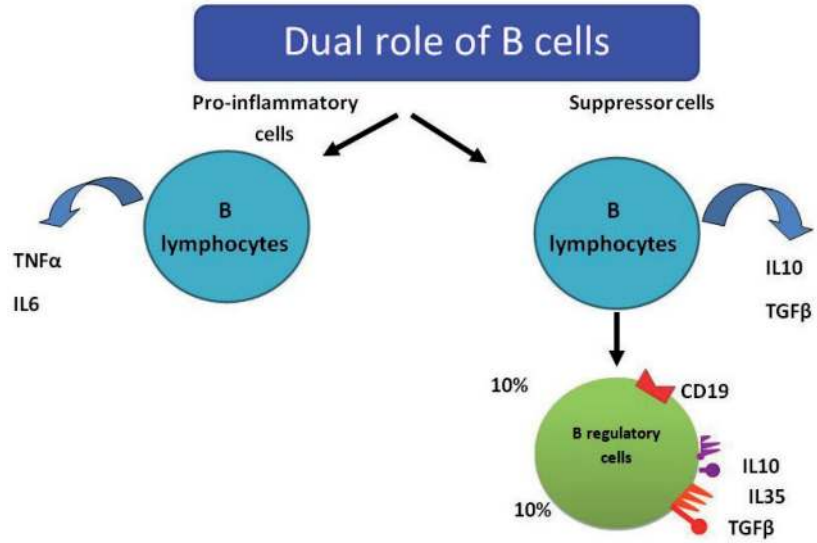

Figure 3.
Dual role of B lymphocytes. 10% of them release IL10, transforming growth factor beta (TGFβ) and interleukin 35 (IL35).

3.1 Autoantibodies

The major markers of Graves' Disease include TSHR-directed autoantibodies (TRAb). TSHR belongs to the family of glycoprotein hormone receptors and stimulates adenyl cyclase (cAMP) through G protein. The cAMP activates all the functions of thyroid cells, e.g. thyroglobulin synthesis, functioning of iodine pump, activity of thyroid peroxidase and release of hormones. Thyrotropin is a physiological agonist for the receptor.

Three types of TSH receptor antibodies can be distinguished:

- stimulating - thyroid stimulating immunoglobulins (TSI), which imitate the receptor ligand and increase the level of adenyl cyclase (cAMP), thus promoting the production of thyroid hormones and the growth of the gland.

- blocking - thyroid blocking immunoglobulins (TBI), inhibiting the activity of TSH and thus leading to hypothyreosis.

- neutral, whose effect on TSH receptor has not been yet examined.

In rare cases, both TSI and TBI are present or they are changed, one into the other, due to treatment. In clinical studies, the level of TRAb can be assessed using methods based on receptor binding (the so called binding assays), used to detect antibodies in the blood that compete with TSH for binding to its receptor (TSH binding inhibitory immunoglobulins, TBII or TRAb). However, in this way it is impossible to differentiate between their biological, stimulating or blocking activity.

The newest method, the so called bioassay (biological tests), is not routinely applied due to high costs. It can be used to determine the level of cAMP production after TSI binding to TSH receptor. The method is also used to monitor thyroid opthalmopathy and in the case of doubtful diagnosis of Graves' Disease due to borderline or negative TRAb values. Currently, no system is available to measure the activity of neutral antibodies. In our patients, TSI and TBI were determined with a

biological test using Chinese hamster ovary cells with an embedded gene encoding the TSH receptor and with the luciferase system. TSI from a sample obtained from a patient binds to the receptor and via cAMP triggers the production of luciferase, thereby initiating a light reaction. The emission is measured with a luminometer. The measured values are compared to the reference values and in this way the presence of antibodies is confirmed or denied. The cut-off point in the analysis using a Thyretain TSI bioassay is the sample-to-reference ratio of more than 140% for the stimulating antibodies, and the degree of inhibition over 40% for the blocking antibodies.

Patients with hyperthyroidism and concomitant Graves' opthalmopathy showed significantly higher values of TSI/TSAb before and during treatment as compared to hyperthyroid patients without opthalmopathy (**Figure 4**). Patients in the prepubertal age had higher levels of TSI/TSAb than those in the pubertal age. Girls had significantly higher values than boys ($p < 0.02$) (**Figures 5** and **6**).

Moreover, the comparison of the proportion of positive values of TSI/TSAb vs. TBII in the whole group of patients with untreated Graves' Disease and

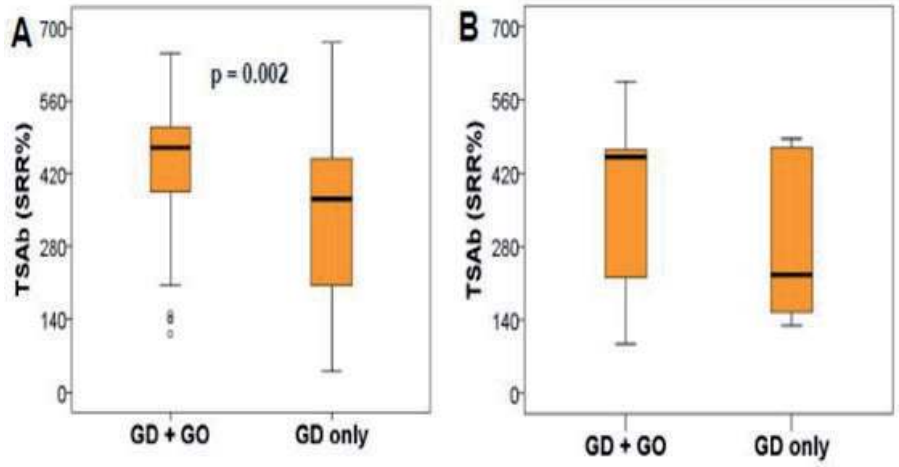

Figure 4.
Levels of thyroid stimulating immunoglobulins (TSAb): (A) untreated children; (B) children treated with Graves' Disease and with or without ophthalmopathy.

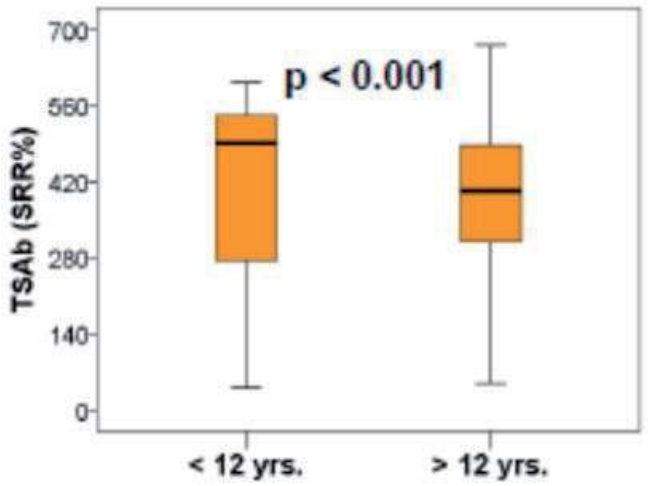

Figure 5.
Levels of thyroid stimulating immunoglobulins (TSAb) in children with Graves' Disease before and during adolescence.

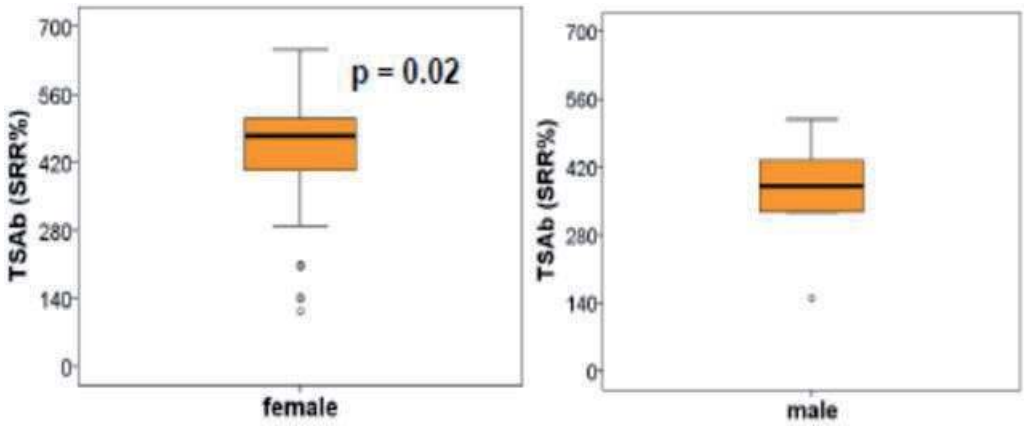

Figure 6.
Levels of thyroid stimulating immunoglobulins (TSAb) in females and males with Graves' Disease.

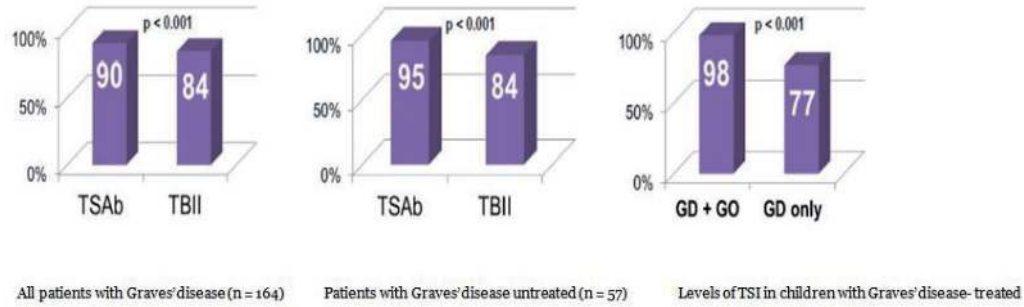

Figure 7.
Comparison of positive values of TSI/TSAb to TBII levels in all patients with Graves' Disease – untreated and with Graves' Disease and ophthalmopathy.

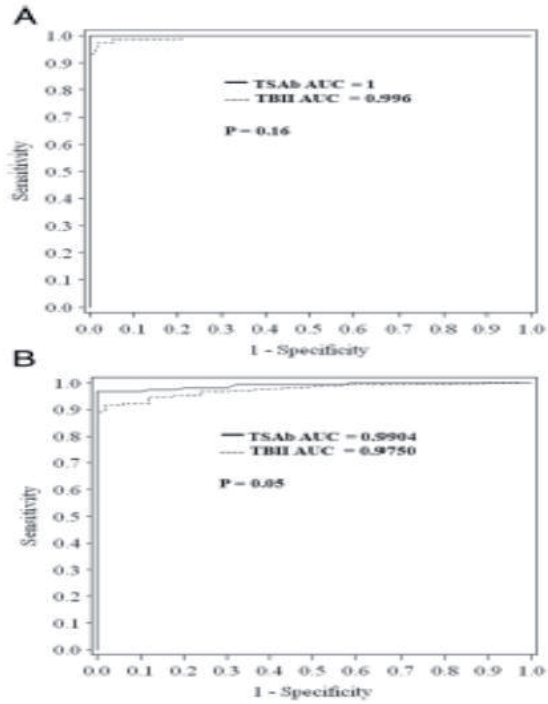

Figure 8.
ROC curves for TSI and TBII levels in patients with Graves' Disease; (A) untreated; (B) treated.

Graves' Disease with concomitant opthalmopathy revealed significantly higher values for TSAb than TBII in each group (**Figure 7**). The ROC curves for TSI and TBII in the above mentioned group of patients with Graves' Disease are presented in **Figure 8**.

Graves' Disease is also characterized by the presence of autoantibodies directed against various components of the thyroid, i.e. antibodies against thyroid peroxidase (anti-TPO), thyroglobulin (anti-TG). However, they are not highly specific and sensitive in the detection of this disease [15–17].

4. Clinical symptoms

Graves' Disease is a chronic disorder characterized by periods of exacerbations and remissions, with a differentiated clinical picture, slightly different in children as compared to adults. In the pediatric population, the CNS shows higher sensitivity to the excess of thyroid hormones and lower to the circulatory system. On the physical examination, the patient presents with restless behaviour and body mass deficiency despite good appetite. The child's skin becomes smooth, warm and moist, and the goiter is the most constant symptom. The thyroid goiter is usually evenly enlarged, with parenchymal density, smooth and painless. On palpation, throbbing and tremour of the gland can be felt, caused by enhanced blood flow, well heard (when auscultated above the thyroid) as a vascular murmur, mainly in the upper poles of the gland. The heart action is markedly accelerated and does not slow down at rest. In hyperthyroidism observed in the prepubertal group the growth rate and bone age advancement are accelerated due to increased release of growth hormone. The excess of thyroid hormones in early childhood is manifested by physical overreaction and concentration disorders. This effect is associated with the particular sensitivity of the CNS to the thyroid hormones, which affect α- and β-adrenergic postsynaptic receptors and increase serotonin release. In the prepubertal Graves' group neuropsychiatric symptoms have been observed including hyperirritability, locomotor anxiety, sleep and concentration disorders, which are manifested as worse academic performance and emotional lability. Ophthalmopathy in children with Graves' Disease is generally mild in nature and ocular lesions subside along with normalization of thyroid hormone secretion. Infiltrative-hydropic exophthalmos is rare. Pretibial edema in the pediatric group has a location similar to that in adults but is different in nature: it is soft and not well separated. **Table 1** presents the effect of hyperthyroidism on the respective systems.

Graves' Disease occurs in children with other autoimmune diseases, such as type 1 diabetes, Addison's disease, albinism, systemic lupus erythematosus, miastenia gravis, juvenile idiopathic arthritis, autoimmune thrombocytopenia, Addison-Biermer anemia. The risk of the disease is increased in children with trisomy 21, Turner syndrome and DiGeorge syndrome. In diabetic children metabolic balance is difficult to achieve. The course of the disease in these patients with concomitant hyperthyroidism is labile and it is difficult to compensate for glycemia. Demand for insulin increases, mainly as a result of developing insulin resistance and fast tissue insulin metabolism. At the same time intestinal glucose absorption is increased, gluconeogenesis is enhanced and glycogen synthesis is decreased. Moreover, in the states of thyrotoxicosis the secretion of growth hormone, which is also responsible for glycemia increase is elevated. In consequence, ketone acidosis frequently develops [1, 2].

Organs	Symptoms
Nervous system	Nervousness, irritability, emotional lability, sleep disturbance, headaches, learning difficulties, trembling of fingers, toes, tongue- fine tremor; motor incoherence, muscle weakness, excessive fatigue, especially of proximal muscles of limbs; reduction of tendon reflexes' duration;
Skin	Smooth, soft, satin skin; increased sweating and moistness; intensified warmth of the skin; vivid dermographism; delicate and breakable hair;
Eyes	Von Graefe's, Kocher's, Stellwag's, Popow's, Dalrynple's, Joffroy's signs- mild symptoms caused by stimulation of the sympathetic nevous system; Moebius' sign- lack of convergence; exophthalmos- bulging of the eye anteriorly out of the orbit;
Bones	Acceleration of growth rate and maturation of bone age in children; final height lower than expected due to early overgrowth of epiphyseal cartilages; intensive decay; limbs' pain; osteoporosis- typical for adults;
Circulatory system	Constant tachycardia; increase of systolic BP, decrease of diastolic BP (high amplitude of blood pressure); heart arythmia- premature atrial contractions, atrial fibrillation (especially in newborns); systolic murmur caused by hyperkinetic circulation; in ECG: increase of QRS amplitude; disturbance of repolarization phase; echocardiography: signs of hyperkinetic circulation;
Digestive system	Increased appetite combined with weight loss; accelerated intestinal passage and increased number of defecations; fatty diarrheas caused by inadequate secretion of pancreatic enzymes due to accelerated gastric emptying and increased intestinal peristalsis; absorption disorders;
Urinary tract	Increased thirst and polyuria due to increased index of glomerular filtration; hypercalcaemia, as the most frequent electrolyte disturbance in hyperthyroidism, impairs antidiuretic hormone activity, disturbs urine concentration and induces renal diabetes insipidus;
Reproductive system	Menstrual disorders; secondary lack of menstruation; decreased libido;

Table 1.
Impact of hyperthyroidism on different systems.

5. Diagnosis

5.1 Medical history and clinical examination

A detailed medical history and thorough clinical examination are indispensable for proper diagnosis. Clinical diagnosis of primary hyperthyroidism is confirmed by elevated levels of circulating thyroid hormones and TSH suppression to the values close to zero. In rare cases of hyperthyroidism, such as thyreotropinoma, ectopic TSH secretion and pituitary resistance to thyroid hormones, serum TSH level is usually elevated or inadequately normal, whereas the levels of thyroid hormones (fT_4 i/lub fT_3) are increased. With autoimmunization in Graves' Disease, the level of anti-TSHR antibodies is elevated. High titer of these antibodies allows for the exclusion of the toxic phase of Hashimoto thyroidits (hashitoxicosis) and subacute thyroiditis. Other antithyroid antibodies (a-TPO and a-ATG) are of minor importance. Very seldom, the co-occurrence of Graves' Disease and hashitoxicosis determines a positive titer of anti-TSHR antibodies.

5.2 Imaging investigations

Imaging investigations- thyroid ultrasound - is a subsequent stage in the diagnosis of hyperthyroidism; however, it is not indispensable for the diagnosis

of Graves' Disease. In autoimmune hyperactivity, the thyroid is usually enlarged, with reduced echogenicity and markedly increased blood flow in color Doppler ultrasound (CDUS) and in power Doppler examination, with moderately increased flow in non-autoimmune hyperactivity caused by active mutation in TSH-R (**Figures 9** and **10**). Currently, due to high access to anti-TSHR antibody titer assays, gland scintigraphy with I^{123} or Tc^{99} is seldom performed. It used to be widely applied to differentiate between Graves' Disease, thyrotoxic phase of chronic lymphocytic thyroiditis, subacute thyroiditis and a hormonally active nodule.

5.3 Other examinations

If nodular lesions coexist, fine-needle aspiration biopsy (FNAB) of the thyroid should be performed. Elastography remains a complementary method to differentiate nodules [18].

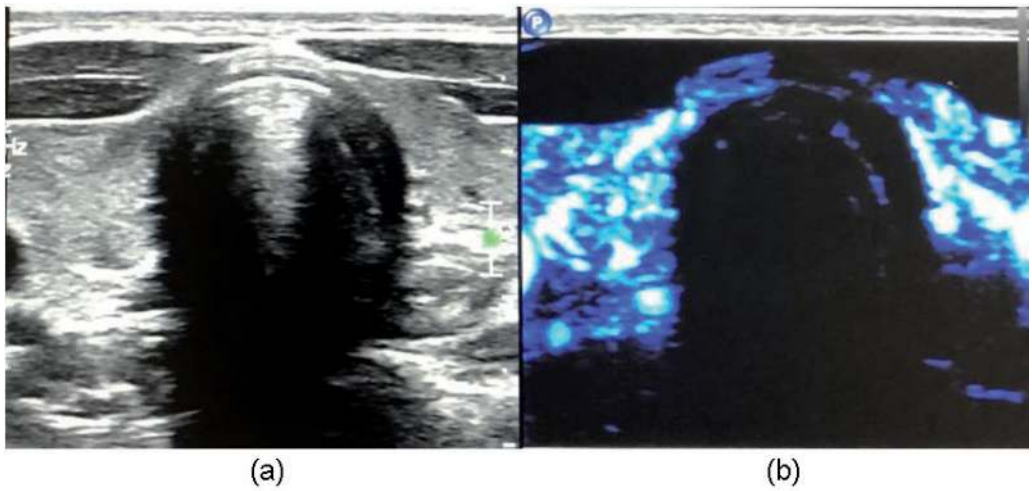

Figure 9.
Ultrasound image of hyperthyroidism in the course of active mutation in TSH receptor: (a) thyroid gland slightly enlarged bilaterally, inhomogeneous, hypoechogenic; (b) moderately increased vascular flow in Doppler ultrasonography.

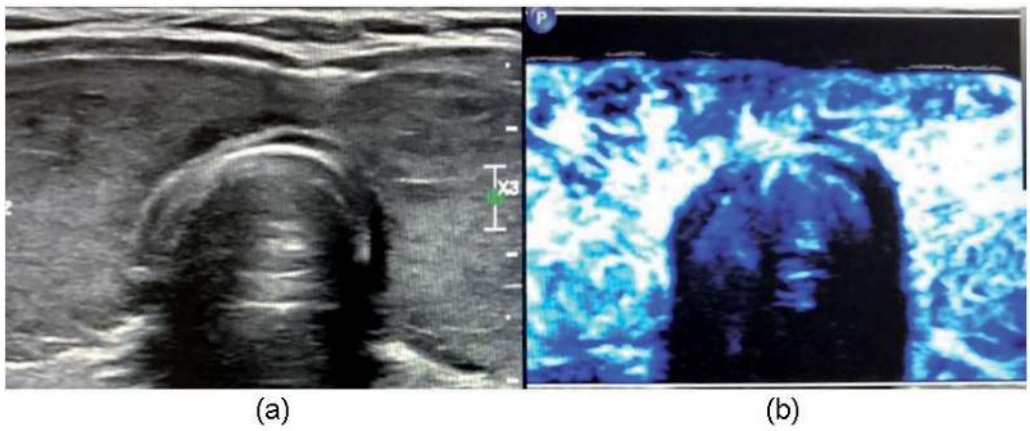

Figure 10.
Ultrasound image of hyperthyroidism in the course of Graves' Disease: (a) thyroid gland enlarged bilaterally, inhomogeneous, hypoechogenic; (b) increased, regular vascular flow in Doppler ultrasongraphy.

6. Treatment of hyperthyroidism

In most common type of hyperthyroidism in children with Graves' Disease causal treatment is unknown. The management involves pharmacotherapy (thyrostatics, β-adrenolitics), although sometimes radical radioiodine I^{131} therapy or surgical treatment is necessary. Some world literature reports indicate the application of immunotherapy in Graves ophtalmopathy in adults using rituximab (monoclonal anti-CD20 antibodies) to delete B cells. Thorough knowledge of the structure of human antibodies stimulating (M22) and blocking (Ki-70) TSHR has given great hope for their immunotherapeutic use in humans, including possible administration of blocking antibodies (TBI) to treat severe thyroid ophthalmopathy in the course of Graves' Disease. In children, conservative treatment with thyrostatics is most frequently used.

In clinical practice, two basic methods are used:

- the so called combined method ("block and replace" regimen), consisting in the inhibition of the production of thyroid hormones with a thyrostatic and administration of levothyroxin at a replacement dose (less recommended currently).

- adaptive method (titration regimen), based on monotherapy with a thyrostatic; smaller doses of the drug are used depending on the levels of thyroid hormones.

6.1 Thyrostatics

It is assumed that treatment with thyrostatics until eutyreosis is obtained usually lasts a few weeks (2–6 weeks), and complete treatment with gradually decreasing doses should be conducted for 24–36 months (**Figure 11A**). When Graves' Disease occurs in the prepubertal period the time of therapy prolons to 3–6 years (**Figure 11B**). In children thiamazoles are administered, namely imidazole, thiamazole (administered in one or two doses; 0.3–0.6 mg/kg/24 h, max. 30 mg/24 h), carbimazole (two or three doses daily; 0.4–0.8 mg/kg/24 h.

Propylothiouracyl, which 12–15 years ago used to be the most commonly administered medicine in the USA in the therapy of Graves' Disease, currently is not recommended and even contraindicated due to increased risk of severe liver damage. FDA reports have indicated that 1:2000 children may develop severe liver failure that will require transplantation as a consequence of propylothiouracyl administration. In 1:200 children reversible propylothiouracyl-dependent liver damage will occur. The only way to avoid liver injury is to withdraw this drug, limiting its use only to patients who are allergic to thiamazole and who have to be prepared to surgery or in children sensitive to thiamazole whose parents do not give their consent to radical treatment, as well as in the first trimester of pregnancy.

A -adrenolitic drug (athenolol 1–2 mg/kg in one dose or propranolol 1–2 mg/kg in 2–3 doses) is also administered for the first 2–4 weeks until euthyreosis is achieved to monitor hyperactivation of the cardiovascular system. Serum levels of fT_3 and fT_4 get normalized after 2–6 weeks, whereas TSH can be inhibited for a few months (3–6 on average). Therefore, in the initial phase of the treatment peripheral hormones should be monitored. Thyroid hormones usually need to be measured after 2 weeks, one month and then every month until TSH normalization. When f T_3 and f T_4 become normal the thyrostatic dose is

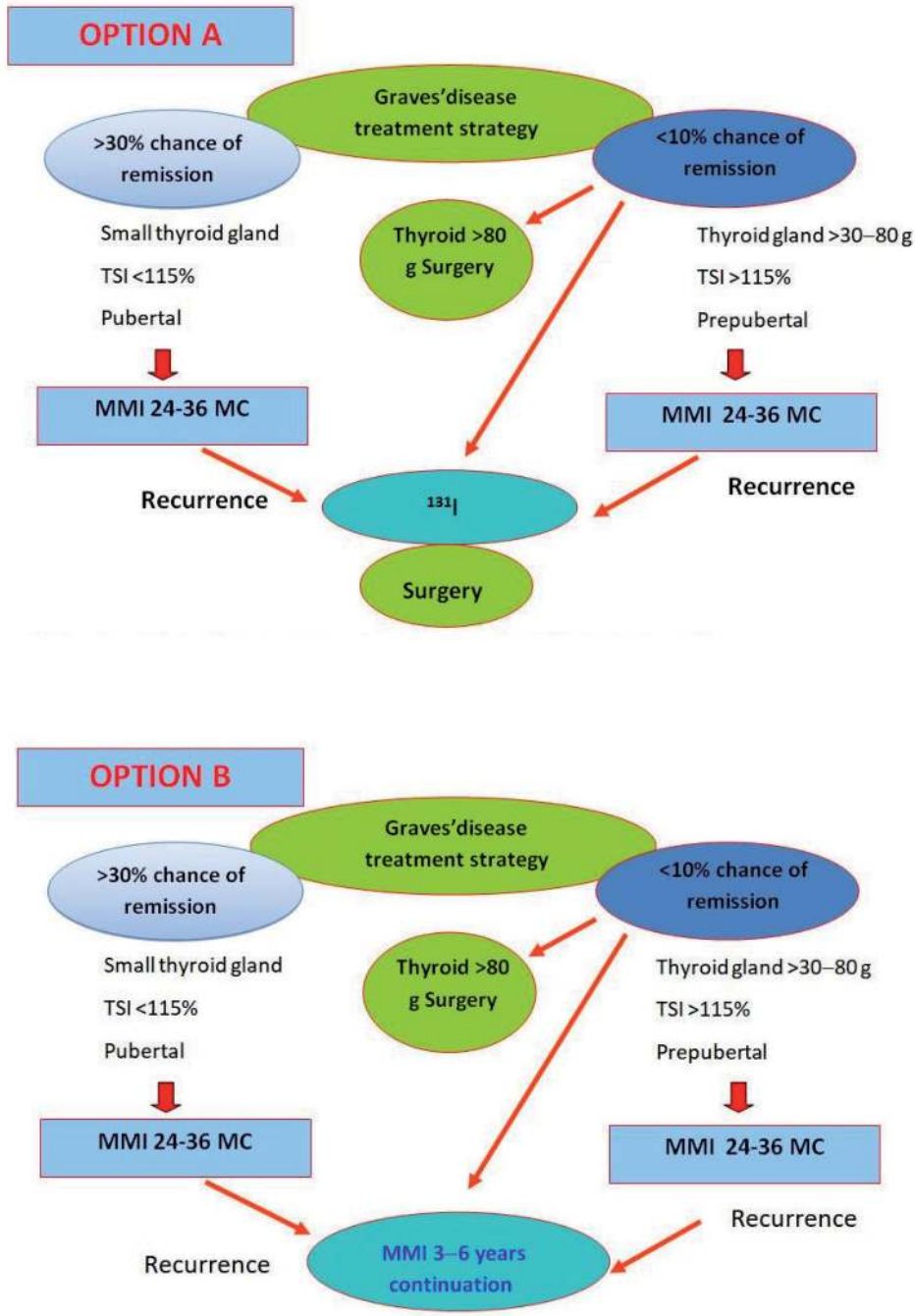

Figure 11.
*(A) Schemes of Graves' Disease treatment strategies: A option (**Figure 11A**) and B option (**Figure 11B**).*
*(B) Schemes of Graves' Disease treatment strategies: A option (**Figure 11A**) and B option (**Figure 11b**). Based on: Léger et al. [1].*

decreased by 30–50%, and then after the subsequent 3–6 weeks depending on the level of the hormones to the maintenance dose of 5–15/24 h. The persistence of antireceptor antibodies and difficulty in obtaining euthyrosis indicate high risk of relapse. Thus, remission is strictly related to the titer of TSI antibodies. When the titer is high, the chance of remission is 15%, and with a low titer approximately 50% of patients enter remission. Therefore, already at the start of the therapy, determination of TSI antibodies may help predict which patients are likely to achieve long-term remission of the disease.

The incidence of side-effects depends on the thyrostatic dose. All antithyroid drugs may cause goiter. Other undesirable effects include skin disorders, such as pruritus, urticarial or erythematosus exanthema, dyspepsia, arthralgia or transitory granulocytopenia (<1500 granulocytes/mm^3).

Agranulocytosis is rare (approximately 0.2% of cases). It should be remembered that as hyperthyreosis may lead to moderately increased neutropenia, complete blood cell count should be done prior to treatment and in any case of fever or strep throat. When the level of neutrophils is <1000/mm^3, the treatment should be discontinued or the dose decreased; at <500/mm^3 – further treatment is contraindicated.

In turn, the level of transaminases should be assessed prior to treatment implementation and possibly when a thyrostatic is introduced. Regular control of liver function is not justified. If symptoms of jaundice, gastrointestinal dysfunction or pruritis appear, measurements should include liver enzymes (ASPAT, ALT), total and bound bilirubin and ALP. Cholestatic jaundice, hepatitis or lupus-like syndrome are rare.

Other side-effects after propylothiouracyl administration include hepato-, neuro- and myelotoxic effects (with thrombocytopenia and agranulocytosis <250 granulocytes/mm^3) and vasculitis with the presence of ANCA antibodies. Thus, in the light of the current knowledge, children should not be treated with propylothiouracyl, and the recommended therapy should be based on thiamazole, radioactive iodine or surgery [19–22].

6.2 Radioiodine therapy

Radioiodine therapy is usually restricted to patients who are resistant to pharmacological treatment and who do not enter remission, or when they develop toxic reaction to a drug or have not complied with doctor's recommendations. The aim of the therapy is total destruction of the thyroid parenchyma by applying an ablative dose and in consequence obtaining permanent hypothyroidism. The advantages include easy application, lack of long-term side-effects and high efficacy of the first dose (approximately 95%). In the relapse of hyperthyroidism the subsequent dose of radioiodine can be administered 6 months after the first dose.

Young age (>5 years) is not a contraindication for this therapy, although much caution is required in children younger than 10. The risk of thyroid cancer in children exposed to I^{131} is the highest in those younger than 5 years due to increased vulnerability of the thyroid tissue to proliferative effects of ionizing radiation and gradually decreases in older age groups. Thus, children receive higher doses of radioiodine, i.e. a constant dose of 15 mCi, or doses dependent on the gland mass and its iodine uptake potential (150–200 μCi/g of thyroid tissue; 5.5–7.4 Mq/g; 12 000–16 000 cGy/g), so that to minimize the risk of secondary neoplasms. The radioiodine therapy should be followed by thyroxin substitution to manage hypothyroidim and avoid TSH increase. There is also no evidence that in the offspring of patients treated with I^{131} due to hyperthyreosis or thyroid cancer the risk of genetic defects is elevated (it is comparable to the risk noted in the general population).

Iodine (I^{131}) is usually administered after a break of 5–7 days in the application of the thyrostatic. Some suggest that antithyroid therapy should not be disrupted and the I^{131} dose needs to be increased by 20% to avoid the risk of an overactive thyroid storm. Otherwise, the use of -adrenolites and antiinflammatory non-steroids should be recommended to attenuate the symptoms of postradiation thyroiditis. Moreover, less common are nausea, pruritis of the neck skin, hypoparathyroidism or exacerbation of Graves ophthalmopathy. In this latter case, even though enhanced opthalmopathy in children is not frequent, protective treatment with glycocorticosteroids

for 6–8 weeks should be considered (some recommend 3 months after radioiodine administration). Prolonged steroid therapy may have an effect on growth cartilage and body mass, and shows immunosuppresive action. Contraindications to radioiodine therapy are at the same time indications for surgery: large goiter >80 g, pressure symptoms, severe thyrotoxicosis with accompanying neurological symptoms, lack of iodine uptake of the thyroid, suspicion of a neopastic lesion, severe ophthalmopathy, age < 5 years, pregnancy and lactation, and also lack of consent to I^{131} treatment.

6.3 Surgical treatment

Surgical treatment of Graves' Disease is the oldest therapeutic method and total thyroidectomy which prevents relapse of hyperthyroidism is currently recommended. However, it is burdened with the risk of retrograde laryngeal nerve injury, hypoparathyroidism and more seldom hypothyroidism relapse (referring to 1–5% of children after total thyroidectomy vs. approximately 10–20% after partial or subtotal thyroidectomy). Sporadically, infection or keloid is observed at the site of the postoperative scar. The risk of complications depends to a large extent on the skills and experience of a surgeon. Importantly, prior to surgery a patient has to be treated with a thyrostatic drug and be in euthyreosis, receive iodide preparations (e.g. Lugol's solution or potassium iodide) 7–10 days before, 3–7 drops, each dose twice daily to reduce thyroid gland vascularity.

6.4 Excision of thyroid tissue

In rare cases of hyperthyroidism in children that is caused by the presence of autonomic tissue, radical treatment with thyroid removal or administration of ablation doses of radioiodine is recommended. In the state of thyroid hormone poisoning, the hormones need to be withdrawn and a -adrenolitic drug, e.g. propranolol, should be administered.

The therapy should be individually tailored and discussed both with the patient and the family [23–26].

7. Conclusions

- The diagnosis of Graves' Disease in children is based mainly on the determination of TSH suppresion and the presence of anti-TSHR antibodies.
- Thyroid ultrasound is not indispensable for the diagnosis; however, it allows for the assessment of the gland size and homogeneity.
- Scintigraphy is not required to diagnose Graves' Disease.
- The measurement of T_4 and T_3 is not obligatory in the diagnosis of Graves' Disease in children, but it is useful for treatment monitoring and to assess the prognosis of the disease relapse.
- Lack of anti-TSHR antibodies may suggest genetically inherited hyperthyroidism.
- The first-line treatment of Graves' Disease in children involves pharmacotherapy with imidazole, carbimazole, thiamazole at the initial dose of 0.4–0.8 mg/kg/24 h (0.3–0.6 mg/kg/24 h for thiamazole) depending on the disease severity to the maximum dose of 30 mg.

- Propylothiouracyl is contraindicated for children.
- Depending on patient's age, disease severity and the presence of anti-TSHR antibodies the initial therapy should last 3–6 years.
- Prior to the treatment implementation, peripheral blood cell count measurement should be performed to assess the grade of neutropenia caused by hyperthyroidism. Regular determination of blood count during check-ups is not necessary.
- Blood count should be performed if the patient is feverish or has strep throat. Neutrophil count <1000/mm^3 is an indication for treatment discontinuation or dose reduction; <500/mm^3 - further treatment is absolutely contraindicated!
- The level of transaminases should be determined prior to treatment. Regular control of liver function is not justified.
- When jaundice, gastrointestinal tract dysfunction or pruritis appear, liver enzymes (ASPAT, ALAT), total and bound bilirubin and ALP should be determined..
- Patients and their parents should be informed about possible side-effects of thyrostatics.
- Patients and their families should be informed about prognosis (50% of patients obtain remission after a few years of treatment) and possibilities of radical treatment.
- Female patients with Graves' Disease (both in the course of remission and after radical treatment) require endocrinology care prior to and during planned pregnancy.
- Indications for radical treatment include contraindications to pharmacology, poor results of pharmacotherapy, repeated prolongation of therapy, parents' and child's request.
- Thyroidectomy is a radical method applied in children before the age of 5 years or in the case of large goiter, nodular goiter or goiter pressing the organs.
- The experience of a surgeon performing thyroidectomy in children is the major factor responsible for postoperative complications.
- Radioiodine therapy is recommended after the age of 5 years if the goiter is not too large (more frequently in puberty).
- Education of patients and parents is important to ensure the best possible response to treatment.

Conflict of interest

The authors declare no conflict of interest.

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