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1. Introduction

Thyroid hormones (TH) are critical for early brain development, somatic growth, and bone and pubertal maturation. Moreover, they are crucial for survival, both in rodents and humans. In many respects, (TH) may be viewed as tissue growth factors. Effects on growth and development are classified as genomic actions mediated via stimulation of mRNA for pituitary growth hormone (GH) synthesis, secretion and sensitivity. TH potentiate GH stimulation of the synthesis and action of insulin-like growth factor 1 (IGF1) and stimulation of the production of different growth factors (epidermal growth factor, nerve growth factor, and erythropoietin). Cartilage response to IGF1 and osteoblastic/osteoclastic bone remodeling are also regulated by thyroid hormones. Unlike insulin and cortisol levels, which fluctuate widely in response to food ingestion and stress, thyroid hormones are typically maintained at a constant level that keeps the metabolic machinery functioning at a proper rate (Zimmerman-Belsing et al., 2003).

In overt hypothyroidism, the severe impairment of linear growth leads to dwarfism, which is characterised by limbs that are disproportionately short compared with the trunk.

Even in subclinical hypothyroidism, a condition of mild thyroid failure, growth velocity in children is suboptimal.

In this chapter, the impact of TH on growth in different forms of hypothyroidism will be discussed in light of thyroid hormone treatment in pediatric praxis.
2. Causes of acquired primary hypothyroidism in childhood

Acquired primary hypothyroidism (AH) in children and adolescents is predominantly caused by end-stage autoimmune disease arising from a chronic autoimmune thyroiditis (CAT). CAT is the most common cause of AH in nonendemic goitre areas, and it afflicts up to 2% of children and adolescents (Bartalena et al., 2007; Fisher, 1990; Raillison et al., 1975; Tomer & Huber, 2009; Fernandez-Soto et al., 1998). Unlike the overt goitrogenic form of CAT, the atrophic form often remains hidden or misdiagnosed for years. Other causes of acquired hypothyroidism include the following: late-onset thyroid dysgenesis and late-onset dyshormonogenesis; decreased responsiveness to thyroid hormones; TSH deficiency; drug-induced, iatrogenic, or endemic iodine deficiency; and chromosomal disorders and cystinosis (Fisher, 1990).

The importance of the thyroid gland for the human body is largely due to its production of hormones necessary for appropriate energy levels and an active life. These products have pleiotropic effects, which include exerting an immense array of hormonal activities (genomic and non-genomic actions) and playing a critical role in early brain development, somatic growth, bone maturation, and mRNA synthesis for more than 100 proteins that constantly regulate the maintenance of all bodily functions. TH impact every tissue to such an extent that a certain degree of thyroid dysfunction is highly likely to result in multiorgan failure thus often mimicking various diseases (Weetman, 2003; Saranac et al., 2011).

3. Genomic and non–genomic actions of thyroid hormones

T3 binding by the nuclear thyroid receptors (TR) leads to responsive gene transcription, which modulates synthesis of mRNA and proteins—which in turn mediate thyroid hormone effects in various tissues. In the central nervous system, general genomic effects include stimulation of cell migration and neuronal cell maturation and stimulation of dendritic arborisation, synaptic density and increased myelogenesis. Gene products regulated by T3 in the CNS are myelin basic protein, nerve growth factors and their receptors, neurotropin 3, neural cell adhesion molecules, cerebellar PCP-2 and prostaglandin D2 synthase (Fisher & Gruters, 2008).

Genomic effects on growth and development include the following: stimulation of pituitary growth hormone (GH) synthesis and secretion; potentiation of GH stimulation of insulin-like growth factor (IGF) synthesis and action; stimulation of growth factor production (epidermal growth factor, nerve growth factor, erythropoetin); and stimulation of bone metabolism/growth (cartilage response to IGF1 and osteoblastic/osteoclastic bone remodelling).

Thermogenic genomic effects include stimulation of mitochondrial enzyme synthesis; stimulation of UCP-1 and UCP-3 in brown adipose tissue and muscle; and stimulation of membrane Na/K ATPase. Metabolic genomic effects include induction of hepatic lipogenic enzymes; stimulation of hepatic glutamine synthetase and α-aminolevulinic acid synthetase; potentiation of prolactin stimulation of lactalbumin synthesis; and potentiation of GH stimulation of β2 euglobulin synthesis (Fisher & Gruters, 2008; Yen, 2001).
The above effects do not occur immediately but only after hours of TR stimulation. However, some TH effects occur immediately (e.g., stimulation of glucose transport and stimulation of adrenergic receptor binding). Additionally, TH can regulate the number of beta-adrenergic receptors in the heart and may thereby enhance sensitivity to catecholamines. Increased catecholamine effects via increased beta-adrenergic receptor binding and post-receptor responsiveness are prominent manifestations of the hyperthyroid state (tachycardia, tremor and lid lag) and are manifested in the face of normal or lowered circulating concentrations of catecholamines (Fisher, 1990).

4. Thyroid hormones and growth plate

The process of longitudinal bone growth is governed by a complex network of endocrine signals, including growth hormone, IGFI, glucocorticoid, thyroid hormone, oestrogen, androgen, vitamin D and leptin (Nilsson et al., 2005). The growth plate consists of three principal layers: the resting zone, proliferative zone and hypertrophic zone. In hypothyroid animals, the proliferative and hypertrophic zones are decreased in height, and chondrocyte proliferation, chondrocyte hypertrophy and vascular/bone cell invasion are affected. In addition, the normal columnar organisation of the growth plate is disrupted (Stivens et al., 2000). Some of the skeletal effects appear to be due to direct action on the growth plate. Growth plate chondrocytes express thyroid hormone receptor (TR) isoforms TR-α, α-1, and β. Most cases of thyroid hormone resistance in humans are caused by dominant-negative mutations of the TR-β gene, which may also affect TR-α function and show variable skeletal effects (Takeda et al., 1992, Nilsson et al., 2005).

TH are critical for normal bone growth and development. In children, hypothyroidism can cause short stature and delayed closure of the epiphyses. Biochemical studies have shown that TH can affect the expression of various bone markers in the serum, reflecting changes in both bone formation and resorption. TH increase alkaline phosphatase and osteocalcin in osteoblasts. Additionally, osteoclast markers such as urinary hydroxiproline, urinary pyridinium, and deoxypyridinium cross-links are increased in hyperthyroid patients. These observations suggest that both osteoblast and osteoclast activities are stimulated by TH (Yen, 2001).

5. Levels of the thyroid hormone control

There are three levels of the regulation of thyroid hormone concentrations and actions: I constant hormonal serum concentration is maintained by a feedback loop between the hypothalamus, pituitary and thyroid. This centrally regulated system is not sufficient to provide the necessary amount of TH for every tissue and cell in the body. II TH for local needs are provided by the control and regulation of TH entrance by active transmembrane transporters and the tissue-specific action of activating enzymes (D1 and D2 deiodinase) and a deactivating enzyme (D3 deiodinase), whose concentrations are regulated differently in each
tissue. III The third level of the regulation of hormonal response depends on the type and activity of TH receptors and is also active at the tissue-specific level. (Bianco et al., 2002; Van der Deure et al., 2010).

Some tissues, such as muscle, have a relatively low deiodinase activity and are dependent, to a great extent, on tri-iodothyronine derived from the thyroid and liver. Other tissues, such as the brain and liver, have a high deiodinase activity, and the availability of tri-iodothyronine is determined within the tissues themselves (Romijn et al., 2003).

Thyroxine-binding globulin (TBG) is the most important carrier protein for T4. In contrast, TBG and albumin seem equally important for T3. The binding reactions are nearly complete, and thus the euthyroid steady-state concentration of free T4 and T3 approximate 0.03% and 0.3% (respectively) of total hormone concentrations. TBG levels are higher in children than in adults and decrease progressively to adult levels during adolescence (Fisher, 1990; Fisher & Grueters, 2008).

6. Different forms of hypothyroidism and their impact on growth

6.1. Central (hypothalamic–pituitary) hypothyroidism

The prevalence of central hypothyroidism approximates 1 in 20,000 births. The most frequent causes of the acquired form are irradiation of the head, chemotherapy for malignant disorders, craniopharyngiomas, granulomatous disease, meningoencephalitis and head trauma. The development of the pituitary gland as well as TSH gene expression is regulated by the multiple pituitary transcription factors. Genetic mutation of these factors has been found to cause familial hypopituitarism with TSH deficiency. The congenital form of central hypothyroidism occurs in anencephaly, holoprosencephaly, septo-optic dysplasia (SOD), medial facial syndromes, TSH β mutations, and HESX1, Pit-1, Prop-1 and LHX3/LHX4 mutations (Kelberman & Dattani, 2008). Congenital central hypothyroidism is also associated with multiple hormonal deficiencies. However, idiopathic forms of hypopituitarism are still often present and hide some forms of autoimmune and congenital disorders (De Graaf et al., 2009).

Growth failure due to GH or TSH deficiency is usually the earliest manifestation of pituitary hypofunction, but other features related to primary disease, neurologic disorder, or hypothalamic dysfunction may be prominent.

Isolated central hypothyroidism is an uncommon disorder associated with short stature in children presenting with low free T4 and normal or low serum TSH concentrations without other evidence of pituitary disease. The diagnosis of central hypothyroidism can be considered in those with a serum free T4 level in the lower half of the normal range and normal TSH concentrations. The TRH test is of diagnostic value in such circumstances.

The prevalence of isolated central hypothyroidism has been reported as 16% in a group of 181 children with idiopathic short stature (Rose, 1995).
In our group of 59 children with growth hormone deficiency, 4 had pituitary dwarfism because of the classic triad (Fig 1): a hypoplastic anterior pituitary, an ectopic posterior pituitary and an invisible or transected pituitary stalk. In 10 children, pituitary structural lesions classified as microadenoma were present on magnetic resonance imaging (MRI) examination (4 microprolactinomas and 6 non-functioning pituitary microadenomas). Two children experienced hypopituitarism after head trauma, and an additional 2 experienced hypopituitarism because of suprasellar tumours (germinoma, Fig 2, and teratoma). In one boy, an empty sella syndrome was revealed.

Figure 1. MRI of boy with central hypothyroidism caused by pituitary hypoplasia.

Figure 2. MR sagittal scan of boy with suprasellar germinoma producing central hypothyroidism (TT4 62.41 nmol/L, FT4 8.32 pmol/L, TSH 0.057 mIU/L).
Hypointense pituitary lesions are an important sign of hypothalamic and pituitary dysfunction and a distinguishing marker in children that should be considered for further investigation and endocrinologic surveillance. Thus, MRI investigation is recommended as an effective screening tool. MRI is an important option for use in further evaluation of short children and resistant obesity accompanied by gonadal dysfunction and pubertal disorders.

6.2. Primary, overt hypothyroidism

The clinical manifestations of acquired hypothyroidism in childhood differ from those in adults. The classic manifestations also occur in children but are not as prominent. Instead, the most important sign of acquired hypothyroidism in childhood is a slowing of growth. Weight tends to increase, and, in most instances, weight for age is greater than height for age. The retardation of bone age in hypothyroidism usually equals or exceeds the retardation in linear growth (Fisher, 1990; Hall, 1989; Saranac & Stamenkovic, 2012). Feeling cold, experiencing fatigue, and displaying primary amenorrhoea with no impairment of school performance is also commonly observed in children with acquired hypothyroidism. However, in some children, deterioration in school work and learning difficulties might occur. Clinical signs of severe acquired hypothyroidism unique to childhood are presented in Table 1. Mixedema, generalised or discrete hair loss and firm, often smooth goitre with a palpable Delphian node on the isthmus are clinical signs of autoimmune hypothyroidism. Clinical markers such as segmental vitiligo, hypopigmented rings surrounding dark naevi (“halo naevi”), leukotrichia, premature greying of the hair, and alopecia areata are all, like typical vitiligo, associated with autoimmune disorders (Hall, 1989). An increased frequency of autoimmune thyroid disorders is reported in Turner syndrome (TS) and other non-disjunctional chromosomal disorders, such as Down syndrome, and these disorders seriously affect growth in these children. Hypothyroidism of autoimmune origin is so common in TS that almost every other TS girl will most likely develop hypothyroidism, with the likelihood increasing with age (El-Mansoury et al., 2005; Mortensen et al., 2009; Testa et al., 2006).

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Table 1. Clinical signs of acquired hypothyroidism unique to childhood (Fisher, 1990)

In primary hypothyroidism, the anterior pituitary shows an increase in thyrotroph cells. Hyperplasia or even adenoma formation may result from long-standing hypothyroidism,
particularly hypothyroidism dating from infancy. Enlargement of the pituitary fossa has been demonstrated, and suprasellar extension of the feedback tumour of the cells may occur rarely (Hall, 1989). We recently published a case of a hypothyroid boy with severe growth failure caused by long-standing, neglected hypothyroidism with very high thyrotropin levels and sella enlargement (Saranac & Stamenkovic, 2012).

In cases of long-standing hypothyroidism, the dose of l-thyroxine should be increased gradually to prevent cardiac failure. Most children respond well to a dose of 100 µg/m² (Fisher, 1990; Fisher & Grueters, 2008). When clinical features such as loss of body hair occur and increase the possibility of pituitary hypothyroidism, it is dangerous to treat the patient with thyroid hormone without determining the plasma cortisol level and, if necessary, correcting any adrenocortical deficiency (Hall, 1989).

In clinical practice, the adequacy of TH supplementation is assessed by the measurement of TSH and fT4 concentrations. This approach deserves two comments. First, it is remarkable that the normal values of TSH show a more than ten-fold variation. In clinical practice, because the optimal TSH concentration within this range for individual patients is unknown, titration of the substitution dose of thyroxine within this variation is relatively crude. Secondly, the intrinsic assumption of many doctors using this approach is that a normal TSH concentration reflects adequate TH concentrations not only at the tissue level of the hypothalamus and the pituitary but also in other tissues. However, it is likely that this assumption is erroneous (Romijn et al., 2003).

Some adults require combined l-T3 + l-T4 treatment, although the benefit in humans is controversial. The rationale for this combined treatment is that monotherapy cannot provide euthyroid state in all tissues of the hypothyroid subject. In rodents, it has been clearly demonstrated that there is no single dose of T4 or T3 that normalises TH concentrations simultaneously in all tissues in hypothyroid animals (Escobér-Morreale et al., 1996). Therefore, it is highly likely that in patients treated with l-T4, subtle derangements at the tissue level are present with respect to TH availability and, most likely, TH action. Unfortunately, we lack sensitive signs and symptoms needed to evaluate this hypothesis in clinical practice, and we do not have sensitive biochemical markers of TH action at the tissue level other than TSH (Romijn et al., 2003).

Unlike insulin and cortisol levels, which fluctuate widely in response to food ingestion and stress, thyroid hormones are typically maintained at a constant level, resulting in a proper metabolic rate. Thyroid hormones are crucial for survival in both rodents and humans (Zimmerman-Belsing et al., 2003). In many respects, thyroid hormones may be viewed as tissue growth factors. Indeed, normal overall whole body growth does not occur in the absence of thyroid hormones despite adequate levels of growth hormone (GH). TH also influence the function of other endocrine systems. After 3 to 4 years of age, thyroid hormone deficiency is not associated with mental retardation but delayed somatic and linear bone growth. Bone maturation, measured as bone age, is also delayed; diaphyseal bone growth is reduced; and epiphyseal growth and mineralisation largely cease. The effects of thyroid hormones on somatic and skeletal growth are mediated by stimulation of the synthesis and action of growth hormone and growth factors (Griffin & Ojeda, 1998).
Thyroid hormones also potentiate growth hormone stimulation of insulin-growth factor synthesis and action as well as GH and IGFs binding to the receptors and post-receptor events. Additionally, TRH’s rise in primary hypothyroidism acts as suppressor of nocturnal growth hormone pulses. In 1989, Chernausek et al. documented the attenuation of spontaneous nocturnal growth hormone secretion in the hypothyroid state and the proportional fall in IGF1 serum concentration.

Catch-up growth is defined as a linear growth rate greater than expected for age after a period of growth inhibition. Growth-inhibiting conditions conserve the limited proliferative capacity of growth plate chondrocytes, thus showing the normal process of growth plate senescence. When the growth-inhibiting condition resolves, the growth plates are less senescent and therefore grow more rapidly than normal for age (Marino et al., 2008; Shao et al., 2006). If the hypothyroid state is prolonged prior to treatment, catch-up growth may be incomplete. Excessive dosage is marked by disproportionate advancement in skeletal age (Fisher & Grueters, 2008).

In 1991, Pantsiouou found that in spite of appropriate treatment, primary hypothyroidism results in permanent growth failure. In girls, normal harmony between growth and pubertal maturation has been disturbed or lost. Growth continued after menarche, but final height remained far below the age average and predicted height according to mid-parental height. That is why some authors, including Minamitani, recommended the combined treatment with GnRH analogues and GH, besides substitutional l-T4 treatment for optimal growth stimulation.

6.3. Subclinical hypothyroidism

Subclinical hypothyroidism (SCH) is defined by an elevation of serum TSH with circulating free thyroid hormone concentrations that are within the reference range (Evered et al., 1973; Cooper & Biondi 2012). SCH is a common issue in clinical practice that predominantly affects women and has a prevalence of between 2 and 10%, which increases in an age-related fashion. More than three-quarters of individuals with SCH have serum concentrations between 5 and 10 mU/l. Although treatment of the mild thyroid failure of SCH with levothyroxine (l-T4) would seem to be a logical approach to management, only a minority of individuals with SCH have symptoms that are typical of hypothyroidism (Pearce et al., 2012). According to one of the few available follow-up studies on juvenile SCH, this may be a benign and remitting process with a very low risk of evolution toward frank hypothyroidism (Raillison et al., 1975; Moore, 1996).

There is great controversy concerning the clinical significance of SCH and whether or when subjects with SCH should be treated with l-T4. In adults, SCH has been associated with several complications, such as progression into overt hypothyroidism, abnormalities of lipid profile, increased risk of atherosclerosis and cardiovascular morbidity and clinical signs and symptoms of mild disease, including impaired cognitive function (Cerbone et al., 2011). Treatment is currently recommended in SCH subjects with a TSH value above
10 mU/l, whereas treatment for TSH levels between 4.5 and 10 mU/l remains a matter of debate (Wiersinga et al., 2012).

In children, SCH is not yet a well-defined condition due to both the low prevalence of this disorder and the lack of long-term studies.

Some children with CAT experience all types of thyroid dysfunction during the natural course of the disease: mild hyperthyroidism at diagnosis (hashitoxicosis), euthyroid state and gradual progression from subclinical to overt hypothyroidism. An intriguing form of CAT could be subclinical hypothyroidism with mixed signs of hypo- and hyperfunction (“autoimmune dysthyroidism”). Thus, clinical features do not always correspond to hormonal status. The reasons for diagnostic pitfalls, including clinical ambiguity, are challenging for pediatricians and endocrinologists (Saranac & Stamenkovic, 2012).

Even though subclinical hypothyroidism is defined as an asymptomatic disorder in which a euthyroid state is maintained due to TSH elevation, in our experience, this dysfunction type actually has clinical expression despite being labelled as mild, subclinical or compensated. Tunbridge recorded clinical features in adults, which included cold intolerance, dry skin, lack of energy, puffiness around the eyes, acroparaesthesiae and weight gain, and the signs elicited included periorbital swelling, scaling of the skin and a slow pulse rate (minor degrees of hypothyroidism) (Hall, 1989). In children, even the subclinical form of hypothyroidism has an impact on growth, weight regulation, bone maturation and pubertal development.

While the mild clinical picture of hypothyroidism is expected in children, the appearance of the opposite hyperfunction signs in subclinically hypothyroid subjects is intriguing. A possible explanation could be the rise in TRH with neurotransmitter properties that leads to release of TSH, PRL, FSH, and noradrenalin (NA). Tachycardia, nervousness, and emotional lability in subclinically hypothyroid subjects could be attributed to NA released in this way. Moreover, the turnover of NA in the brain of hypothyroid subjects has been found to be elevated (Jovanovic-Micic et al., 1991; Bauer et al., 2008).

The ambiguity in the clinical picture could also be explained by the presence of heterogenic antibodies to the TSH receptor in the same subject. A transient shift from blocking to stimulating antibodies may provoke hyperthyroid signs in the hypothyroid subject (Song et al., 1996; Saranac et al., 2003, 2010).

Reasons not to treat SCH in adults are numerous. Serum TSH is not a perfect marker of thyroid hormone action because of its dependence on hypothalamic TRH, type 2 deiodinase, and the influence of steroids, cytokines, adipokines and neuromediators (e.g., l-dopa). Increased TSH is not a fixed and immutable parameter: it varies according to diurnal, circannual, and physiological and non-thyroidal factors. Normal values of TSH can differ ten-fold within normal reference values. Obesity is a circumstance in which high levels of TSH are frequently discovered, although a lack of thyroid hormone is not generally the culprit. Furthermore, therapy with levothyroxine is not free of inconven-
ience and risks. Finally, extreme longevity is associated with increased serum thyrotropin levels (Pearce et al., 2012).

In growing child, there are scarce data regarding the evaluation of substitution benefits. Thus, the dilemma of whether to treat subclinical hypothyroidism is still in question. The problem is further complicated by the fact that obese children do present with elevated values of TSH. Several mechanisms leading to hyperthyrotropinaemia have been hypothesised, including increased leptin-mediated production of pro-TRH, impaired feedback due to a decreased number of T3 receptors in the hypothalamus, and variations in peripheral deiodinase activity (Radetti et al., 2008). With respect to growth in SCH, there are ambiguous data. In a prospective evaluation of the natural course of idiopathic subclinical hypothyroidism in childhood and adolescence, Wasniewska et al (2009) did not find any association between TSH changes and FT4 values, clinical status or auxological parameters. The study group consisted of 92 patients (50 boys) with idiopathic SCH. The majority of the patients (88%) normalised or maintained their TSH levels during the 24-month follow-up period. Stature was within normal limits at diagnosis and remained normal at the end of the study. In a cross-sectional controlled study, Cerbone et al (2011) evaluated growth and intellectual outcome in 36 children with persistent SCH who had never been treated with levothyroxine and in the same number of age- and sex-matched controls. The authors concluded that persistent SCH in children is not associated with alterations in growth, bone maturation, BMI, and cognitive function or other complaints that could be ascribed to SCH even after several years. However, the mean duration of follow up was only 3.3 years.

In 17 paediatric patients with SCH, Ergur et al. (2012) documented poor performance on tests measuring attention and neurocognitive capabilities. No significant differences were found between the SCH group and the healthy controls in verbal fluency and encoding tests. In a small study of 16 children with SCH and diagnosis of CAT, we found suboptimal growth velocity (4.12 cm/year), which significantly improved up to 7.36 cm/year (p<0.05) after 12 months of treatment. Mean bone age advancement was 1.6 years/year and did not exceed growth acceleration (1.98 years/year), due to careful dose monitoring. Despite appropriate treatment with l-T4, the mean SD score of height for chronological age remained unachievable in comparison with euthyroid, non-treated CAT patients (Fig 3). During treatment, the T3/T4 ratio in the treated group showed a sharp rise after 1 year of treatment, in accordance with the mean best growth velocity during follow-up period of mean 2.19 years (range 1-4 years) (Fig 4). The mean TSH of the SCH group was 8.98 mU/ml at diagnosis, falling gradually to 4.81 mU/ml after 1 year and 1.98 mU/ml after 2 years of treatment. We concluded that children with SCH had suboptimal growth before treatment, which improved during l-T4 substitution, with simultaneous normalisation of TSH levels. In addition to other favourable effects on thyroid volume and thyroid autoimmunity markers, TH isohormonal therapy provides optimal growth in children with CAT. However, caution is recommended in children who are simply obese, where, despite elevated TSH, l-T4 treatment should be avoided or cautiously considered.
7. Conclusion

Screening for congenital hypothyroidism achieved the historical goal of eliminating the most serious endocrine cause of mental retardation, hypothyroid cretinism. However, acquired
hypothyroidism remains a frequent cause of interruption of statuto ponderal progress, failure to thrive and growth impairment. Dynamic growth is a fundamental characteristic of happy, healthy children who are well nourished and nurtured. Stature represents a phenotypic characteristic that produces significant anxiety in children and their families. A euthyroid state is crucial in this complex, synergistic process in which nutrition, emotions and hormones act simultaneously. Growth is a reflection of thyroid function. Thus, the first step in the hormonal investigation of children with growth failure is the thyroid function assessment. Pediatricians must be educated to select patients suspected of hypothyroidism, to document different forms of hypothyroidism and to treat them properly while simultaneously being attentive to false positive results.

Although hormonal substitution therapy in the treatment of hypothyroidism is extremely successful and has fulfilled its promises, a perfect mimicry of endocrine homeostasis by thyroid hormone replacement is, in general, impossible, especially in growing children.

Acknowledgements

Supported by a grant from the Ministry of Science of Republic of Serbia, No 41018. We are grateful to Mr Mile Randjelovic for excellent technical assistance.

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