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Different Faces of Chronic Autoimmune Thyroiditis in Childhood and Adolescence

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1. Introduction

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, exerting an immense array of hormonal activities, playing a critical role in early brain development, somatic growth, bone maturation, and mRNA synthesis for more than a hundred proteins that constantly regulate the maintenance of each and every bodily function. They also have critical effects on energy metabolism and on the metabolism of nutrients and inorganic ions. To such an extent is every tissue impacted in one way or another by thyroid hormones that a given degree of thyroid dysfunction is highly likely to result in multiorgan failure, this often mimicking different diseases (Saranac et al., 2011).

2. Chronic autoimmune thyroiditis as multifaced disease

Chronic autoimmune thyroiditis (CAT) is multifaced disease. Its incidence has increased dramatically over the past few decades afflicting up to 2% of the general population. CAT as autoimmune disorder results from a complex interplay of genetic, environmental, and endogenous factors. Genetic factors are predominant and likely account for aproximately 80% of the liability to develop autoimmune thyroid disorders (AITD). However, at least 20% is due to environmental factors. The mechanisms whereby environmental factors may affect the onset and the course of AITD are, in many instances, obscure or, at least, incompletely understood, but gene-environment interaction seems a fundamental process for the occurrence of AITD (Weetman, 2003; Bartalena et al., 2007). In children, CAT is the most common cause of acquired hypothyroidism in nonendemic goitre areas (Fisher, 1990; Raillison et al., 1975; Tomer & Huber, 2009). Unlike overt goitrogenic form of CAT, atrophic one remains hidden or misdiagnosed for years. The clinical manifestations of acquired hypothyroidism in childhood differ from those in adults. The classic manifestations also occur in children, but are not so prominent (Table 1). Instead, the most important sign of acquired hypothyroidism in childhood is growth failure (Table 2). 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, 1999; Hall, 1989). Herein we present two cases of atrophic CAT with long course and delayed diagnosis.

Lack of energy	Hoarseness of the voice, slow speach	Hearing loss
Cold intolerance	Typical facial appearance	Uveal effusion
Acroparaesthesiae	Prolongation of the tendon reflexes	Muscle cramps
Dryness of the skin	Myxedoedematous, xantochromic skin	Muscle stiffness
Weight gain	Slowing of all intellectual funtions	Anorexia
Constipation	Diminished memory and somnolence	Ascites, pleural effusion
Bradycardia	Enlarged, indolent, dilated heart,	Pericardial effusion
Anaemia	Shortness of breath	Menstrual disorders
Infertility	Other endocrine dysfunction	Exocrine dysfunction

Table 1. Clinical signs of overt hypothyroidism

Growth retardation
Bone age retardation
Muscle hypertrophy pseudohypertrophy
Sexual disorders
Delayed puberty
Precocious puberty

Table 2. Clinical signs of acquired hypothyroidism unique to childhood (Fisher, 1990)

Segmental vitiligo, hypopigmented rings surrounding dark naevi ("halo naevi"), leucotrichia, premature greying of the hair, and alopecia areata are all, like typical vitiligo, associated with autoimmune disorders and are asigned as clinical markers of autoimmunity (Hall, 1989).

3. Examples from clinical praxis of overt, late diagnosed hypothyroidism in children

3.1 Case 1

A 14- year-and-7-month-old boy in pubertal age, but with no signs of pubertal development was referred to endocrinologic examination because of short stature. At admission his height was only 127 cm (- 4.3SD), his height age was 8 years with proportional delay in bone maturation. Muscular pseudohypertrophy and dry, xantochromic skin were present. His appearance was apathetic with an emotionally flat affect. Muscular pseudohypertrophy of solar muscles was present and this phenomenon has been referred to as the Kocher-Debre-Semelaigne syndrome. The hormonal status showed the hypothyroid state; low levels of TT4 and TT3 and extreme elevation of TSH level suggestive of feedback pituitary adenoma. The sella turcica was enlarged and the rare radiologic signs of neglected hypothyroidism were present: osteosclerosis of the skull base and "motocyclist's sunglasses sign" (Fig. 1). In addition epiphyseal dysgenesis and delayed bone maturation were observed (Fig. 2). Ultrasound scan showed atrophic thyrod gland. The severe impairment of linear growth led to dwarfism, characterized by limbs that are disproportionately short compared with the trunk. Besides the growth retardation, the child appeared younger than his age because of sexual infantilism (Fig. 3). The treatment with Na-l-thyroxine accelerated growth and resulted in normal final height and allowed for pubertal progression. This catch-up growth was adequate to compensate the preexistant growth retardation (Fig. 3).

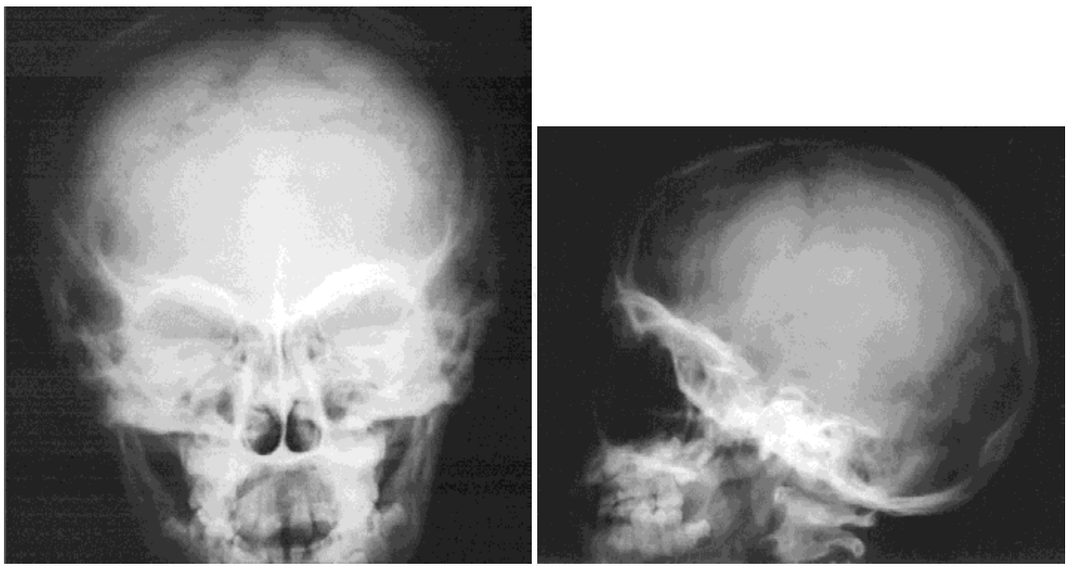

Fig. 1. Cranial radiologic image of the patient with neglected hypothyroidism.

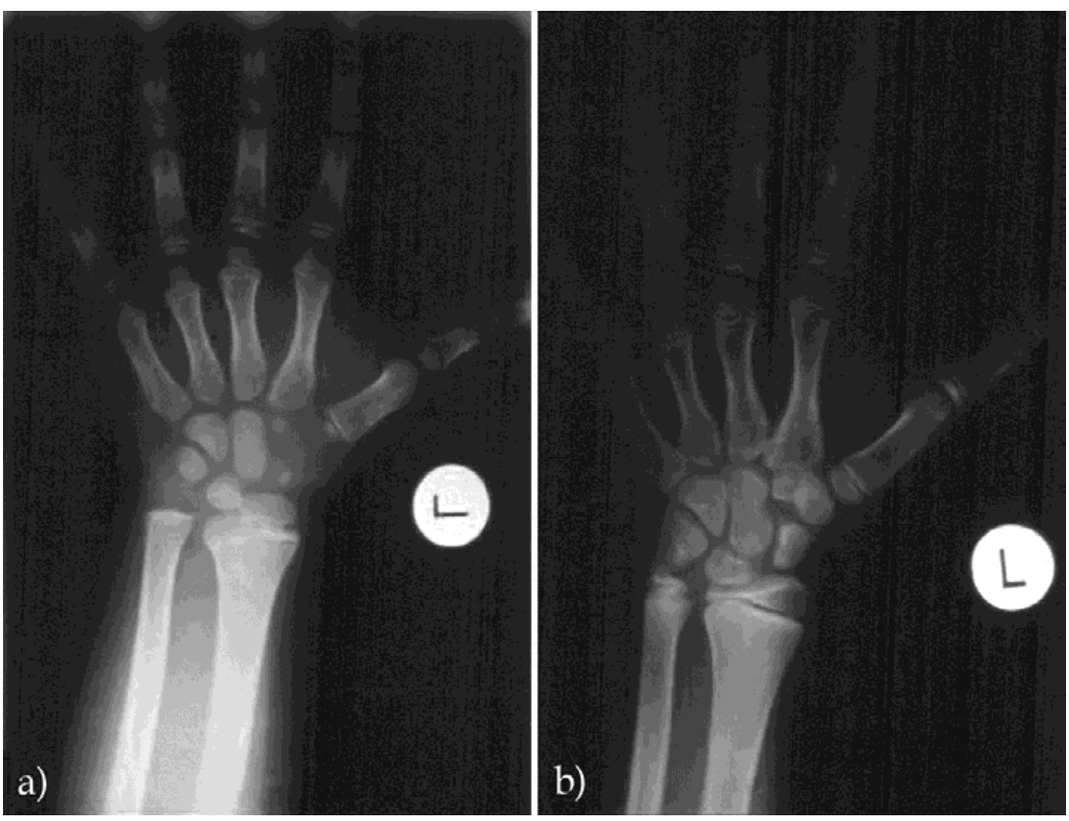

Fig. 2. Bone age retardation of hypothyroid patient (a) corresponds to 8 years versus chronological age of 14 years and 7 months. The treatment allowed for faster bone maturation (2 years for a year) (b).

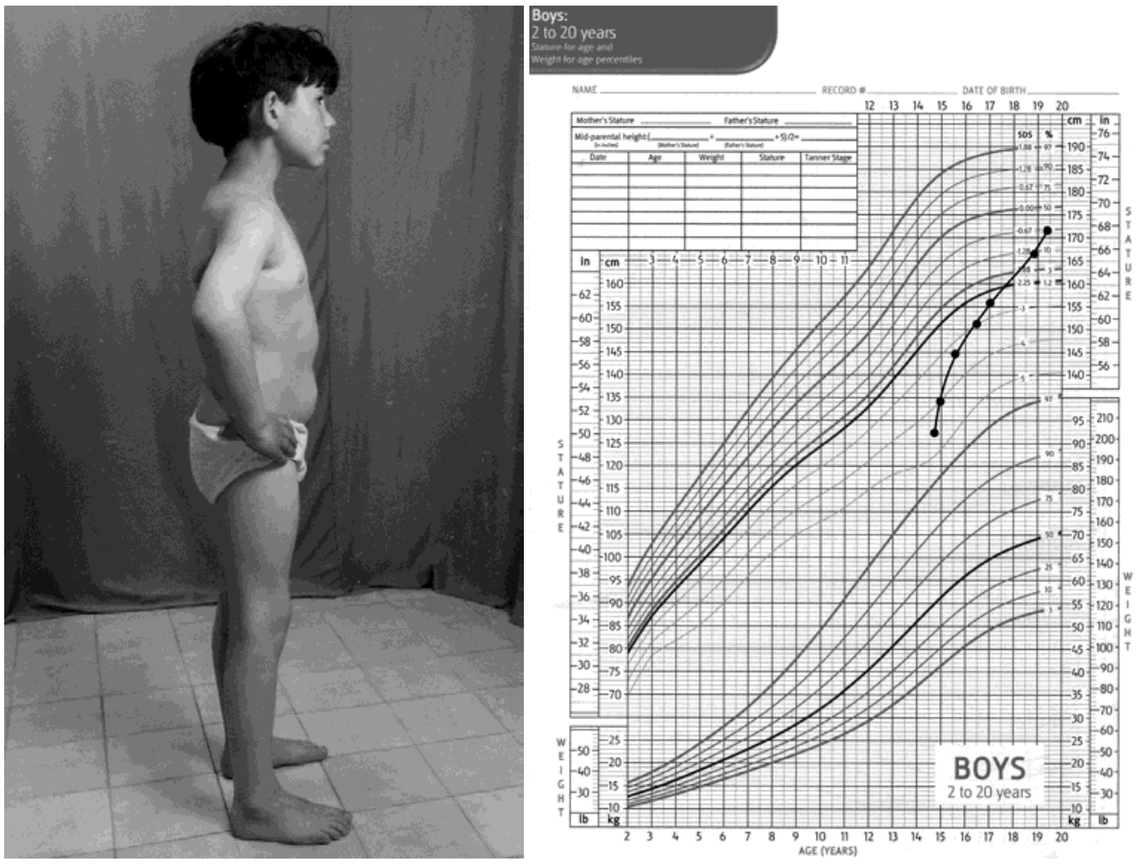

Fig. 3. Disproportionately short stature with pubertal delay and growth curve of the Case 1.

3.2 Case 2

In adolescent girl the diagnosis of atrophic CAT was overlooked and she was treated as exogenous form of obesity and liver disease. At admittion she was 13 years old, inert, apathetic, bradicardic and with dry skin. Weight gain during past 2 years was reported and she was put on unrewarding diets. Her height of 160 cm was within normal rang, P75 (+0.67), height age was 14 years, calculated ideal weight for heigt was 50 kg, so her body mass (BM) of 66kg showed +16 kg, BMI 26 kg (P95) corresponding to clinical obesity. The most prominent laboratory findings were elevated liver enzyms (oxalacetic and piruvic transaminase), lactat dehydrogenase and creatinin phosphokinase as well as triglycerids (Table 3). HBsAg Hepatitis C antigen was positive. A significant association between hepatitis C and AITD has been found (Fernandez-Soto et al., 1998; Testa et al., 2006). The treatment with hepatoprotectors and diet was obviously unsuccessful. After diagnosis of CAT with acquired hypothyroidism and introduction of thyroid hormone replacement therapy, simultaneously with maintenance of euthyroid state, liver enzyms normalized. Ultrasound image showed small gland with inhomogene structure and hypoechogenic zones (Fig. 4).

Glutamic oxalacetic transaminase	172 IU/l	TT4	23.04 nmol/l
Glutamic piruvic transaminase	269 IU/l	fT4	0 nmol/l
Creatinine phosphokinase	1291 mU/ml	TT3	0.21 nmol/l
Lactat dehydrogenase	677 mU/ml	fT3	0.52 pmol/l
Triglyceride	2.61 mmol/l	TSH	102 mU/l
Cholesterol	5.48 mmol/l	TPO Abs	>1000
		Tg Abs	>1000

Table 3. Laboratory data of the case 2.

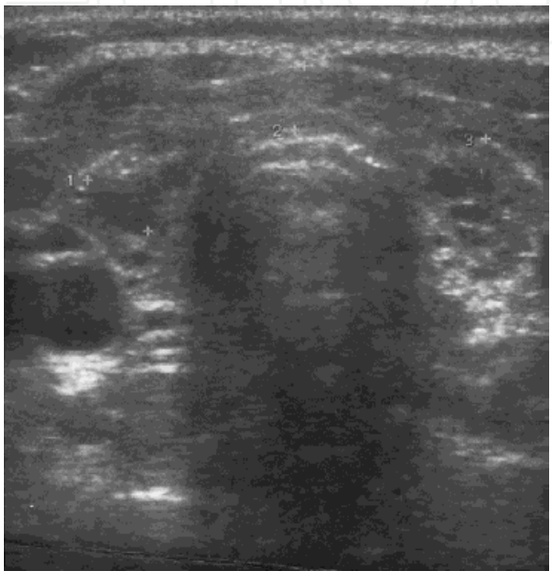

Fig. 4. Ultrasound trasphersal scan of the thyroid in atrophic CAT.

Both cases are illustration of thyroid hormone effects in almost all tissues in the body. Because the long-standing hypothyroidism the dose of Na-l-thyroxine was increased gradually to prevent cardiac failure. Most children respond well to the dose of 100 μg/m^2 body surface (Fisher, 1990; Fisher & Grueters, 2008). When clinical features, such as loss of body hair, raise the possibility of pituitary hypothyroidism, it is dangerous to treat the patient with thyroid hormone without checking the plasma cortisol and if necessary correcting adrenocortical deficiency (Hall, 1989).

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 running in a proper metabolic rate. Thyroid hormones are crucial for survival both in rodents and humans (Zimmerman-Belsing et al., 2003). In many respects thyroid hormones may be viewed as tissue growth factors. Indeed, normal overal whole body growth does not occur in the absence of thyroid hormones despite adequate levels of growth hormone (GH). They 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, also is 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 growth hormone and growth factors synthesis and action. Thyroid hormone dependent effects known to be mediated by stimulation and acumulation of mRNAs coding for specific proteins include GH synthesis in pituitary cells, selected enzymes and proteins in liver, (including malic enzyme), beta-myosin heavy chain synthesis in cardiac tissue and Na/K-ATP-ase in a variety of tissues (Fisher, 1990; Fisher & Grueters, 2008). Growth hormone synthesis by pituitary cells is known to be thyroid hormone dependent. Other peptide growth factors besides insulin-like growth factors (IGF-s) may mediate the thyroid hormone effects on specific target tissues; epidermal growth factor, nerve growth factor and erythropoetin (Griffin, 1988; Fisher, 1990). 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 postreceptor events. Additionally TRH rise in primary hypothyroidism acts as suppressor of nocturnal growth hormone pulses. Chernausek and al. in 1989 documented the attenuation of spontaneous growth hormone secretion in hypothyroid state and proportional fall of IGF-I 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 growth 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).

3.3 Subclinical hypothyroidism

Some children with CAT expirience all thyroid dysfunction types during natural course of the disease: mild hyperthyroidism at diagnosis (hashitoxicosis), euthyroid state and gradual progression from subclinical to overt hypothyroidism. Another 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, beacause of clinical ambiguity are chalanging for pediatricians and endocrinologists.

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

While the mild clinical picture of hypothyroidism is expected in children, the appearance of opposite, hyperfunction signs in subclinicaly hypothyroid subjects, is intriguing. Possible explanation could be the rise of TRH with neurotransmiter properties that leads to release of TSH, PRL, FSH, and noradrenalin (NA). Tachycardia, nervouseness, emotional lability in

subclinicaly hypothyroid subjects could be attribued to NA released in this way. The turnover of NA in brain of hypothyrod subjects is elevated (Jovanovic-Micic et al., 1991; Bauer et al., 2008).

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

4. Conclusion

CAT attracts clinician's attention for decades. Despite of a rapidly growing body of evidence on complexity of etiopathogenesis and clinical presentation of AITD, primary care physicians neglect or misdiagnose CAT. We believe that it is particularly important to draw attention to this problem in pediatric patients. An improved understanding of CAT clinical diversity could yield better diagnostic and treatment pathways.

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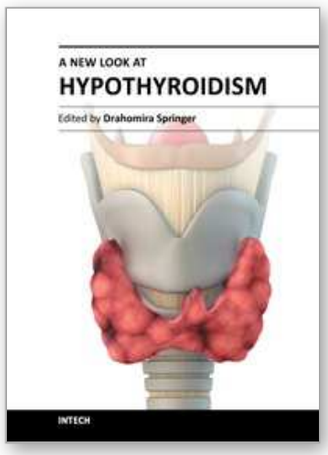

A New Look at Hypothyroidism

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Hypothyroidism is the most common thyroid disorder. It can cause a variety of changes in women's menstrual periods, reduce their chances of becoming pregnant, as well as affect both the course of pregnancy and the neuropsychological development of babies. During pregnancy there is a substantially increased need for thyroid hormones and a substantial risk that a previously unnoticed, subclinical or latent hypothyroidism will turn into overt hypothyroidism. The thyroid inflammation caused by the patient's own immune system may form autoimmune thyroiditis (Hashimoto's thyroiditis). Congenital hypothyroidism (CH) occurs in approximately 1:2,000 to 1:4,000 newborns. Nearly all of the developed world countries currently practice newborn screening to detect and treat congenital hypothyroidism in the first weeks of life. "A New Look at Hypothyroidism" contains many important specifications and innovations for endocrine practice.

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