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Differences in the auxological characters of children with short stature – Differential diagnostic possibilities of hypothyreosis

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ABSTRACT

This study aimed to define the differences in growth characteristics in the three most frequent causes of growth retardation – growth hormone deficiency, hypothyreosis and constitutional delay of growth and development – in order to provide diagnostic means for distinguishing these disorders. The study included 166 children with growth disorders aged 4–18 years. The height for age, the bone age using the TW3 method, the predicted height as the target height and the current prediction using the TW3 method were studied. For bone age, the radius, ulna and short bones compartment (RUS) and carpal bones (CARP) were evaluated separately and the difference in their delay in relation to chronological age (ΔBA_RUS_CARP) was determined. The relationship of the studied variables with sex and the underlying diagnosis was tested and the relationship of hypothyreosis and growth data was estimated. The model was tested on the growth data of 104 randomly selected patients with a growth disorder. The largest significant distinction was demonstrated by the difference ΔBA_RUS_CARP in hypothyreosis. The created linear regression model was highly statistically significant ($\chi^2 = 19.4$, $p < 0.0001$) and showed high selectivity (0.609, 95% CI 0.409; 0.808) as well as high specificity (0.864, 95% CI 0.781; 0.946). The clinical validity of the model demonstrated a 61% predictive value for the detection and an 81% successful specification of hypothyreosis. The study demonstrated the possibility of distinguishing suspected hypothyreosis from other causes of growth retardation based on differences in severity of the ossification delay in skeletal compartments of the hand.

Introduction

Growth is a complex process that is influenced by a number of internal and external factors. Under physiological conditions, the growth of children demonstrates high stability given by a genetically conditioned growth pattern with a predicted population growth position (Czerwinski et al., 2007). Short stature is defined as growth below the 3rd percentile of the population growth norm, or as –1.5 SDS below the genetic growth curve associated with a growth velocity below the 10th percentile or long-term below the 25th percentile of the age norm (Oostdijk et al., 2009; Rose et al., 2005). A hormonal disorder as the cause of growth restriction occurs only in 1–2% of children. All other cases involve either a constitutional variant of growth (up to 80%) or manifestations of some chronic systemic disease (15%). Insufficient growth may be also a component of certain genetic syndromes or bone dysplasiae (approx. 1%) (Waldman and Chia, 2013). Growth is also negatively affected by unfavourable environmental factors, especially those related to the low socio-economic level.

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In a number of diagnoses involving short stature, auxological variables demonstrate a very similar clinical picture – short stature compared to the growth references, growth below the genetic growth curve, borderline or low growth velocity compared to the average for a given age, delayed bone maturation, final predicted height at the low end or below the genetic growth chart as well as delayed sexual maturation during puberty (Oostdijk et al., 2009; Rose et al., 2005). Usually, a more detailed distinction is not possible on the basis of individual markers and assessment of their mutual combinations is more informative. Determination of the bone age is the most informative character. This is most reliably determined by estimating bone age based on plain radiographs of the hand and forearm, as these demonstrate a high correlation with linear growth as well as with sexual maturation at puberty. They also directly reflect the regulatory activity of the principal hormonal axes on the child's overall growth (Gilsanz, 2010; Murray and Clayton, 2013; Tarim, 2011). This is very important especially in the diagnosis of childhood endocrinopathies, as assessment of the degree of development of individual sections of the hand radiograph may indicate in which direction diagnosis should proceed. Separate evaluation of the individual sections of the hand and distal epiphyses of the forearm bones is possible using the Tanner-Whitehouse 3 – TW3 method (Tanner et al., 2001), which evaluates the compartments – radius, ulna and short bones (RUS), ossifying according to the model of long bones with the dominant influence of the somatotropic hormone axis and carpal bones (CARP), ossifying according to the model of short bones with a significantly higher role of the thyroid axis. In diagnoses involving short stature, a characteristic presentation may be observed depending on the severity of the retardation of these compartments compared to chronological age. The greatest disproportion was observed in decreased thyroid gland function (hypothyroidism) (Basset and Williams, 2003; Gogakos et al., 2010; Murphy and Williams, 2004). The aim of this study was to analyse the differences between routinely monitored growth and development markers in the three most frequent causes of short stature – hypothyreosis, growth hormone deficiency and constitutional delay of growth and development. Then, on the basis of these defined differences, the study aimed to develop a diagnostic predictive model of the causes of growth disorder or rather a screening model for suspected hypothyreosis.

Materials and methods

One hundred and six boys and 60 girls aged from 4 to 18 years were included in the study conducted between 2007 and 2013. All were patients of the Institute of Endocrinology in Prague and all had been referred for assessment of growth. Three basic diagnostic categories with a very similar auxological presentation were chosen: (1) hypothyreosis (subclinical forms and euthyroid states), (2) growth hormone deficiency (complete and partial), and (3) constitutional delay of growth and development. The frequency characteristics of these groups are detailed in Table 1.

The auxological data of 104 randomly selected patients with a growth disorder (aged 5–16 years) treated at the Institute of Endocrinology in Prague between 2012 and 2015 were used to test the validity and diagnostic ability of the created predictive hypothyreosis model. Inclusion of all patients and the anonymous processing of their data were approved by the Ethics Committee of the Institute of Endocrinology in Prague before the study was initiated. The research meets the conditions of the World Medical Association Declaration of Helsinki.

Strict criteria for patient selection were defined in order to guarantee maximum homogeneity of the individual samples. Hypothyreosis (hypoT): subclinical form defined as thyroid-stimulating hormone (TSH) levels above the upper limit of the age-specific norm, free thyroxine (fT4) levels within the range of the age-specific normal values; eufunctional state defined as TSH and fT4 levels within the age-specific norm according to the reference range of Heil et al. (2004): age up to 1 year – TSH (mUI/l) = 1.36–8.80, fT4 (pmol/l) = 13.90–26.10; age 1–6 years – TSH (mUI/l) = 0.85–6.50, fT4 (pmol/l) = 12.10–22.00; age 7–12 years – TSH (mUI/l) = 0.28–4.30, fT4 (pmol/l) = 13.90–22.10; 13–18 years – TSH (mUI/l) = 0.27–4.20, fT4 (pmol/l) = 13.60–23.20. Both groups of patients had normal levels of circulating thyroid hormones and the regulatory effect on target tissues was identical.

Complete growth hormone deficiency (GHDC) was characterised by a low level of insulin-like growth factor 1 (IGF-1) compared to age, insufficient stimulated secretion of growth hormone (GH) in 2 standardised tests (arbitrary value up to 5 μg/ml or 10 mIU/l). Partial growth hormone deficiency (GHDP) characterised by a lower level of IGF-1 compared to age, insufficient stimulated secretion of GH in at least 1 standardised test (result just below10 μg/ml or 20 mIU/l). In patients above the lower age limit for the interval of puberty onset (boys over the age of 9 years, girls over the age of 8 years), oestrogen priming was indicated three days before the test in both sexes using an oral dose of 2 g daily. All cases of growth hormone deficiency (GHD) involved the idiopathic form of the disease with no organic cause detected. The radiographs and auxological data were acquired after the diagnosis of GHD had been made but before substitution treatment was started.

Constitutional delay of growth and development (CD) was determined auxologically as delayed growth and bone age with a growth prediction within the range of the genetic growth disposition. The diagnosis was determined *per exclusionem* once all pathological causes were ruled out. The influence of low weight on growth delay was eliminated.

Table 1
The frequency of patients, according to sex and diagnosis.

Diagnosis	Type	Boys (*n*)	Girls (*n*)	Total (*n*)
Hypothyreosis		24	24	48
Growth hormone deficiency	Complete	30	11	41
	Partial	20	4	24
Constitutional delay of growth and development		32	21	53
Total		106	60	166