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Approach to Children with Growth Disorders

Jan Lebl*

Department of Paediatrics, Charles University, Europe

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***Corresponding author:** Jan Lebl, Department of Paediatrics, Faculty of Medicine, Charles University, Prague, Czech Republic, Europe

Abstract

Child`s growth is an orchestrated pre-programmed process. According to the concept of Karlberg, the child`s growth consists from three components - infantile (from intrauterine period up to 2nd birthday), childhood (up to onset of puberty) and pubertal (up to final height). Prerequisites of normal growth include sufficient nutrition, good general health status (absence of long-term inflammatory process), optimal oxygenation of tissues and normal hormonal regulations- regarding growth hormone, sexual hormones, thyroid hormones and hormones of adrenal cortex. Abnormalities of skeletal development and metabolism (skeletal dysplasias) may lead to disproportionate short stature.

Besides of the basic recognition of chronic conditions compromising growth, the main interest of pediatric endocrinologists is given to growth hormone secretion and function. Growth hormone deficiency may be either congenital (genetic or idiopathic), of perinatal origin (e.g., breech delivery) or acquired (brain tumor, brain irradiation). The cornerstone for understanding the genetic background of pituitary hormone deficiencies was laid by Prof. Illig in 1971. She proposed that some children with severe congenital isolated growth hormone deficiency may suffer from deletion of gene encoding human growth hormone (later named GH1 gene). She has observed that these children tend to produce antibodies against growth hormone after initiation of growth hormone replacement- due to the lack of immunological tolerance towards the GH molecule. She assigned these patients as having "A-type of isolated growth hormone deficiency", later known rather as isolated GHD type 1A.

Nearly two decades later in 1988, the first transcriptional factor was identified to regulate differentiation of specialized pituitary cell lines. It was originally assigned as GHF-1, subsequently as PIT1 and recently as POU1F1. POU1F1 governs the final phase of differentiation of pluripotent pituitary cells into somatotrophs, thyreotrophs and lactotrophs. Within the past 25 years, the understanding of genetic determination of pituitary morphogenesis, differentiation and function précised. We are now well aware that pituitary development is governed by a pre-programmed activation of a cascade of transcription factors that orchestrate firstly the pituitary morphogenesis in context with development of mid-line brain structures, optic nerves and eyes, and thereafter differentiation of five cell lineages of the anterior pituitary. Therefore, congenital multiple pituitary hormone deficiency (MPHD) may result from mutations of genes encoding a variety of transcription factors. These include mutations in PROP1, POU1F1, HESX1, LHX3, LHX4, OTX2, SOX2, SOX3, and GLI2. Of these, defects in PROP1 and POU1F1 genes encoding for transcription factors PROP1 and POU1F1 were most prevalent in populations studied so far and may account for up to 25% of all congenital cases of MPHD.

Whereas the specific phenotype of POU1F1 defect is characterized by a severe combined deficiency of growth hormone (GH), thyrotropin (TSH), and prolactin (PRL), usually recognized within the first years of life due to severely retarded postnatal growth, the endocrine phenotypes of HESX1, LHX3, LHX4, and PROP1 defects overlap and have been reported to include failure of up to all five cell lineages of the anterior pituitary. Moreover, especially in PROP1 defect the pituitary dysfunction may evolve throughout the human lifespan and a new hormonal deficit (especially ACTH deficiency) may appear years after the initial investigation. In addition, some of those with PROP1 defects may pass through a period of pituitary hyperplasia during their first two decades of life. The pituitary mass seen at magnetic resonance is benign, did not require surgery in any case of those observed so far and tends to resolve spontaneously. Unnecessary surgeries were provided in some patients who were diagnosed with a PROP1 defect thereafter, when testing became available. Multiple additional signaling pathways are involved in regulation of child's growth, besides of pituitary development and function, and novel genetic mechanisms are being clarified every year. Of those most fascinating, the RAS-MAPK signaling pathway is one of the most complex, opening new insights into genotypes and phenotypes of Noonan syndrome, LEOPARD syndrome, von Recklinghausen disease and some other conditions.

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