Genetic and Hormonal Regulation of Children's Growth

MUDr. Jan Vosáhlo

Abstract

Growth in childhood is a complex process of changing the body, which can be disrupted by various illnesses including endocrine disorders, particularly growth hormone deficiency. Tumors or other processes affecting hypothalamic-pituitary area can be a postnatal cause of GHD; prenatal causes include 1) developmental disorders of the pituitary as part of complex syndromes, 2) developmental disorders of the pituitary due to defects in regulatory genes and 3) defects in genes involved in the synthesis and secretion of GH.

The first topic of the thesis was septo-optic dysplasia - a complex syndrome involving optic nerve hypoplasia, structural brain abnormalities and pituitary dysfunctions. We extensively described phenotype in 11 Czech patients; we observed both complete SOD and incomplete forms variously combining two of the three main components of the syndrome. The cohort then became a part of an international study of 68 patients, in which we studied the phenotype in dependence on the brain morphology. We found correlation between the severity of clinical symptoms and the degree of septum pellucidum abnormities and also a correlation between hippocampus and falx abnormities and neurological symptoms.

As the second topic we studied genes regulating pituitary development (*HESX1*, *PROP1* and *POU1F1*) in a group of 74 patients with combined pituitary hormone deficiency and a detailed phenotype of the found mutations. After DNA extraction and amplification of coding regions we screened for mutations using dHPLC and confirmed them using direct sequencing. We identified a dominant-inherited mutation in POU1F1 gene in one patient and recessive mutations in PROP1 gene in 18 patients whose phenotype was then investigated in detail. We observed TSH and PRL deficiency diagnosed at the same time as GHD and ACTH deficiency developing later in life. Growth of the patients was slightly affected prenatally; growth failure progressed in the first years of life. The age distribution of morphologic

findings on the pituitary supports the theory that the pituitary becomes hyperplastic in early childhood and then regresses spontaneously.
The third issue solved was validation of mathematical models predicting growth during GH replacement therapy on an independent cohort of 38 patients. With the exception of the model for the first year of treatment including GH stimulated values and the model for the sixth year of treatment, the other models tended to underestimate height velocity, which can be explained by more severe GHD, less expressed role of genetic factors on the short stature of patients and higher frequency of GH injections in our cohort.

Keywords

growth hormone, growth hormone deficiency, septo-optic dysplasia, *HESX1*, *PROP1*, *POU1F1*, growth predicting model