Etiology, pathophysiology and postnatal therapy of intrauterine growth restriction with persistent postnatal growth failure

Abstract

Approximately 5% of children are born with a birth weight and/or length less than -2 SDS if compared to normative values for their gestational age and sex. These are referred to as small for gestational age (SGA). This condition results from intrauterine growth restriction (IUGR). The causes of SGA/IUGR can be exogenous, maternal, placental or endogenous - usually caused by a pathogenic genetic variant in the fetus. Approximately 90% of SGA/IUGR children develop a catch-up growth within the first two years of life, while the remaining 10% do not. These children are referred to as SGA-SS (small for gestational age with short stature). The main aim of the project was to investigate the genetic aetiology of SGA-SS in a unique large cohort of 176 children treated with growth hormone at the Department of Pediatrics, Motol University Hospital. Children with a striking phenotype were subjected to targeted testing (karyotype/FISH/MLPA/targeted Sanger sequencing). All others underwent MS-MLPA to identify Silver-Russell syndrome, and those with no genetic etiology yet identified were subsequently screened by whole-exome sequencing or a targeted panel of 398 growth-related genes. Genetic variants were classified using guidlines suggested by the ACMG. Genetic etiology was elucidated in 74/176 (42%) children. We demonstrated that the growth plate plays a central role in growth control. In addition, genes of the GH-IGF-1 axis and of the thyroid axis, as well as genes responsible for intracellular regulation and signaling, are important. Among them was a patient with a very rare premature aging syndrome - Hutchinson-Gilford progeria. In the next part of the project, we investigated the importance of the acid-labile subunit (ALS) of the IGF-1/IGFBP3/ALS ternary complex in the diagnosis and treatment of children with growth failure. In 511 children with growth hormone deficiency (GHD) and/or SGA-SS, we analyzed the levels and correlation of all three components of the ternary complex and the effect of growth hormone treatment on each component. Sanger sequencing in children with low ALS levels did not show a pathogenic or other variant in the *IGFALS* gene. Measurement of ALS levels is not effective for detecting *IGFALS* mutations. Growth hormone increases ALS levels, but biochemical determination of ALS has only insignificant added value for diagnosis and monitoring of children with short stature. The following subproject concerned the effect of growth hormone treatment in a subgroup of SGA-SS children with a pathogenic variant of the *NPR2* gene, which encodes the natriuretic peptide receptor type 2. *NPR2* gene variants have

been shown to cause short stature in approximately 5% of children with familial short stature and their response to growth hormone treatment is promising. In another sub-project we analysed the effect of growth hormone treatment in 397 children with SGA-SS who reached final height from the Czech national database of growth hormone recipients REPAR. By the end of treatment, most patients reached a height above -2 SDS, within the range of normal population values. In these patients, we evaluated the influence of prepubertal and pubertal growth components on the overall effect of growth hormone treatment. The prepubertal component of growth is the main determinant of the treatment effect; therefore, close monitoring of growth in children born with SGA and early initiation of treatment in infancy is of crucial importance. Studies in children with growth failure also included participation in an international multicentre clinical trial to assess treatment with somatrogon, a new long-acting growth hormone administered once weekly. Using standardized questionnaires, a significant reduction in subjective perceived burden for the child and family was found to be one-third in a group of 87 children when treated with somatrogon compared to daily growth hormone injections.

All of these studies have provided original new insights into the etiology, diagnosis, and treatment of children with growth disorder, particularly SGA-SS children.

Key words: Growth; growth genetics; SGA-SS; acid-labile subunit; *NPR2*; somatrogon