

Intrauterine Growth Retardation and Postnatal Growth Failure Associated With Deletion of IGF-1

The authors report the case of a 15.8-year old boy referred for evaluation of short stature and growth delay in whom a diagnosis of GH insensitivity was suggested because of elevated basal and poststimulation GH levels, absent response to rhGH treatment, and low serum IGF-1 concentration. The patient was born at 37 weeks gestation with symmetric IUGR. His birth weight, length, and head circumference were 3.9, 5.4, and 4.9 SD below the mean, respectively. The placental weight was 1.3 SD below the mean. The patient had severe growth failure throughout infancy and childhood. At age 8 years, he underwent evaluation, which showed normal thyroid function tests, normal male karyotype, and elevated serum basal and peak GH levels (18 ng/mL and 94 ng/mL, respectively) after the administration of the clonidine. He received rhGH treatment for 1.7 years, starting at age 11 years, with no effect on his growth rate. IGF-1 levels performed at age 14 years were markedly below normal range (0.05 U/mL, normal for age = 0.48 to 2.8 U/mL). The patient was diagnosed with profound bilateral sensorineural deafness, moderately delayed motor development, hyperactivity, and short attention span. Additionally, some dysmorphic features were recognized, including micrognathia, bilateral ptosis, low hairline, and bilateral clinodactyly. The patient's parents were first cousins once removed. His father, mother, and 10-year-old sister had less severe growth impairment, with heights 1.8, 1.4 and 1.0 SD below the mean, respectively. Subsequent endocrine tests performed on the patient showed normal fasting blood glucose, thyrotropin, prolactin, and cortisol, and pubertal levels of DHEAS although pubic hair was at Tanner Stage 1. The gonadotropin response to GnRH was pubertal (patient was at Tanner Stage 2 for genitalia). The testosterone response to hCG was significant, and the GH peaks on the overnight GH secretion test were supernormal. A normal basal level of 2.2 ng/mL, but high poststimulation of

61 ng/mL levels of GH, were present. There was an absent response of IGF-1 in the generation test and normal IGF-2, IGFBP-3 and GHBP levels. Brain MRI studies were essentially normal, and electrophysiology studies of the CNS were also normal. Detailed DNA studies using PCR and reverse transcriptase PCR were able to identify homozygosity for the D12S346 polymorphism, consisting in the partial deletion of the IGF-1 gene at the level of the exons 4 and 5, and heterozygosity for such polymorphism in both parents and his sister. Both parents and his sister had low-normal levels of IGF-1 and normal IGF-2 and IGFBP-3.

Woods KA, et al. *N Engl J Med* 1996;335(18):1363-1367.

Editor's comment: *It has been known that GH has no direct impact on intrauterine growth. Indirect evidence suggests that insulin, IGF-1, and IGF-2 are the possible mediators of intrauterine growth. This report yields evidence for the pivotal role of IGF-1 in the process of intrauterine and postnatal growth. Unfortunately, this patient was not treated with IGF-1 to ascertain the growth response to this hormone. The coexistence of postnatal growth failure with a history of IUGR should prompt us to think of problems in the expression or action of IGF-1. IUGR patients who do not exhibit catch-up growth need to be assessed, as was this patient. Another interesting finding of this case is the description of less severe growth retardation in the parents and the sister of the proband, all of whom had normal levels of IGF-1, IGF-2, and IGFBP-3. We must ask: "How many individuals do we see with moderate growth failure and without definitive GH alterations who might be cases of heterozygous deletions of portions of the IGF-1 gene?"*

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Newborn Screening Fact Sheets

The Committee on Genetics of the American Academy of Pediatrics has developed and published fact sheets regarding newborn screening that are very useful resources for physicians dealing with children who have metabolic disorders. These guidelines were designed to help physicians understand and interpret the various tests employed for newborn screening. They take into consideration the variations in screening procedures in different states, and give information concerning early detection, treatment, and follow-up of infants with metabolic disorders. For the purpose of counseling and referral, the information also covers the identification of asymptomatic "carrier couples."

The availability of newborn screening is discussed, and professional and public educational materials are suggested. References for additional reading, notes on early hospital discharge, and costs in each state also are provided.

There is detailed information about biotinidase deficiency; maple syrup urine disease; congenital adrenal hyperplasia; congenital hypothyroidism; cystic fibrosis; galactosemia; homocystinuria; phenylketonuria; sickle cell disease; toxoplasmosis; and tyrosinemia. For each condition, the following are reviewed: State Newborn Screening Availability; Brief Clinical Description; Genetics (including chromosomal map location, incidence, inheritance, racial and ethnic variability,