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From the Endocrine Society Meeting, June 13, 1996
**GH Axis – Child and Adolescent:
 A Review of the Clinical Oral Session**

Eight papers were presented. The first was entitled, *IUGR and Postnatal Growth Failure in a Patient Homozygous for a Partial IGF-1 Gene Deletion* (OR 46-1).¹ The first case of a partial insulin-like growth factor 1 (IGF-1) gene deletion was described in a human. The patient was a 15-year-old boy with a birth weight of 1.37 kg at 37 weeks gestation and a height standard deviation score (SDS) of -6.9 at 15 years of age. He was resistant to exogenous growth hormone (GH), had sensorineural deafness and moderate mental retardation. Serum GH was elevated, and IGF-1 was practically nonexistent. Partial deletion of the IGF-1 gene is compatible with life. IGF-1 is important in prenatal and postnatal growth and possibly in central nervous system development.

The second was entitled, *Dwarfism of Sindh: A Novel Form of Familial Isolated GHD Linked to the Locus for GHRHR* (OR 46-2).² Eighteen dwarfs in Pakistan inherited an autosomal recessive GH-releasing hormone receptor (GHRHR) defect, with phenotypes resembling GH deficiency (GHD) or GH insensitivity. GH, IGF-1, IGF-binding protein-3 were low and failed to increase with GHRH or other pharmacologic stimuli for GH release. An inactivating mutation in the GHRHR appears likely on the basis of LOD scores.

The third paper (OR 46-3) dealt with the correlation of hormonal circadian rhythms with types 1 and 3 procollagens. PICP (type 1) increased

markedly, following GH pulsations, and decreased markedly following cortisol elevation.³ PHINP (type III) did not change. The findings suggested that PICP levels in the morning may be low due to morning cortisol elevation, and time standardization is important when evaluating this test. By inference, interpretation of PICP levels may be hazardous because of marked fluctuations over brief periods.

The fourth paper (OR 46-4) dealt with intranasal use of GHR peptide as a therapeutic agent. GHR peptide in short, GH-sufficient children produced a modest average increase of 2.1 cm/yr during 9 to 10 months of treatment.⁴ The emphasis was not on growth, but a fall in the GH released over time to intranasal hexarelin, which occurred without a fall in the initial IGF-1 increased levels. The effective intranasal dose for GH release was 20 times the intravenous dose required. Hexarelin was given three times daily.

The fifth presentation was entitled, *Contrasted Doses of GH to GHD Patients in Respect to Achieving Respectable Adult Heights* (OR 46-5).⁵ Doses of 0.06 to 0.19 mg/kg/wk given to GHD patients with spontaneous puberty produced no gain in height SDS during puberty. Doses of 0.3 mg/kg/wk continued through puberty advanced the mean SDS from -2.1 ± 1.4 at initiation of puberty to 0.9 ± 1.2 at completion of puberty. The larger dose more closely simulates the secretion rate of

GH during puberty, when GH release in the normal adolescent is stimulated by sex steroid secretion.

The sixth presentation was entitled, *Catch up Growth and Height Achievement in Older, Late-Treated GHD Patients* (OR 46-6). It pertained to GHD children >15 years of age who were minimally or not sexually developed when treatment was instituted.⁶ Their mean bone age was 12.2 ± 1.8 years. Year 1, 2, and 3 growth rates with treatment were 8.5 ± 3.1 cm, 7.2 ± 2.3 cm, and 6.0 ± 2.0 cm, respectively. The conclusions were that over the 3 years, improvement of height age (3.2 ± 1.2 years), height SDS (2.3 ± 1.1 SD), and Bayley-Pinneau predicted height (0.9 ± 1.4 SD) were observed. Two patients over 20 years of age, who were sexually infantile, responded similarly.

The seventh paper was from a collaborative European study, entitled *Four Years of GH Therapy in 3 Dosage Regimens in 216 Children With ISS* (OR 46-7).⁷ The conclusions were that GH at 3.0 or 4.5 IU/m² (1.0 to 1.5 mg/m²) resulted in a doubling of the height velocity during the first year. Increasing the dosage after the first year (3.0 to 4.5 IU/m²) reduced the waning growth effect. Growth and final height prognosis improved during 4 years of GH therapy. This was better with 4.5 IU/m² than with 3 IU/m².

The eighth presentation, a report from European collaborators, dealt with long-term response to rhGH treatment in Turner syndrome (OR 46-8). One hundred ninety patients were studied. The Europeans concluded that a 5.0-cm increment (corrected) was added with GH treatment, with wide individual variation. A significant discussion ensued regarding the effect and necessity of beginning GH therapy earlier than the ≥ 9 years of age (average) for patients in the reported study.

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Abstracts From the Literature

Short Stature Caused by a Mutant Growth Hormone

The authors studied a 4.9-year-old boy with short stature (height, -6.1 SD below mean for age and sex) whose growth was normal in utero. Basal and stimulated secretion of immunoreactive growth hormone (GH) was normal but levels of bioactive GH were subnormal. He responded to the administration of GH with an increase in growth rate. Isoelectric focusing was performed, and 2 GH peaks were detected in the proband in comparison to 1 peak in normal subjects. Examination of the *GH-1* gene revealed a heterozygous mutation (guanine to cytosine transversion) of 1 GH gene allele at codon 77 in exon 4, with substitution of cysteine for arginine. This mutation is near a controlling point for the binding of GH to its receptor. Thus, the patient had 2 species of GH, 1 wild-type and 1 mutated form. A similar heterozygous mutation was found in the father, who was of normal height but who had 1 serum GH peak by isoelectric focusing. Further analysis of the mutated GH expressed in *Escherichia coli* revealed that it had normal immunoreactivity compared with wild-type GH, but that it bound to the extracellular domain of the GH receptor (ie, the GH-binding protein) 6-fold more avidly than did native GH. Since this mutated GH did not stimulate intracellular signaling pathways in IM-9 cells, which have GH receptors, it inhibited the biologic effects of wild-type GH in this system. The investigators suggest that the mutated form of GH impaired growth by antagonizing the effects of the native GH molecule, which was also synthesized and secreted by the patient. The reason why

the father with the same heterozygous mutation in the *GH-1* gene did not express this abnormal allele was unexplained.

Takahashi Y, et al. *N Engl J Med* 1996;334:432-436.

Editor's comment: *In the last few months there has been great interest in children with idiopathic short stature (ISS). Partial GH insensitivity among patients with ISS was described earlier (J Pediatr 1995;127:244-250, published in abstract form in GGH Vol 11[4]:8). This was followed by the description of specific mutations of the GH receptor gene associated with ISS (N Engl J Med 1995;333:1093-1098, published in abstract form in GGH Vol 12[1]:14 & 15). Now, Takahashi et al describe a mutation in the GH gene itself that produced an abnormal GH and was clinically associated with short stature in the affected individual.*

These papers provide data heralding a new subset of patients in whom GH gene mutations or GH receptor abnormalities explain the bioactivity of GH. The prevalence of these abnormalities in children with ISS is unknown. Moreover, the features that clinicians should follow to identify GH insensitivity or bioactivity also are not clarified. The diagnosis of these conditions continues to be based upon esoteric, highly sophisticated biochemical assessments.

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