

## Efficacy and Safety of Growth Hormone Treatment in Children With Prior Craniopharyngioma: An Analysis of the Pharmacia and Upjohn International Growth Database (KIGS) From 1988 to 1996

This article presents data regarding the use of human growth hormone (hGH) in children with craniopharyngioma. Extensive data (collected from 1988 to 1996) were extracted from the Pharmacia and Upjohn International Growth Database. The database showed that 488 patients had a prior history of craniopharyngioma (280 boys, 208 girls). The modality of treatment of craniopharyngioma was known in 451 cases: 251 were treated with surgery alone; 144 had surgery plus irradiation; 12 received only irradiation; and 44 had received no surgery or radiation. hGH treatment was begun at a median time of 1.56 years (mean,  $2.23 \pm 1.88$  years) after tumor diagnosis and was given in a mean dose of  $0.49 \pm 0.15$  IU/kg/wk (0.15 mg) in 3 to 7 injections. Of the group, 40.4% were treated with hGH alone, but others received hydrocortisone and other replacement hormones.

Three hundred ninety-four children completed 1 year of hGH treatment; 152 who were prepubertal at the start of treatment completed 5 years of hGH treatment. The median height SDS increment was 0.9 after 5 years. The gain in height SDS was not influenced by tumor recurrence. Bone age increased 4.5 years in 5 years. Seventy-eight males and 53 females who completed hGH treatment to ultimate height were at a median height SDS of -0.7; 58.8% were above -1 SD in relation to target height. Mean height velocity during the final year of hGH treatment was 4.3 cm/y. Adverse effects included tumor recurrence, with 63 recurrences in 54 patients (11%) after a median of 3.7 years after the initial diagnosis; the longest interval between initial diagnosis and tumor recurrence was 10.3 years.

The authors point out that the response of children with treated craniopharyngioma to exogenous GH was similar to that seen in idiopathic growth hormone deficiency. Growth over 5 years was not influenced by the recurrence of tumor. They also state that they were unaware in every case of the factors involved in the decision to discontinue hGH, but that final height had not been achieved in many of these individuals at that time. Finally, they point out that the recurrence rate of 11% is greater than the rate of 6% to 7% reported in the National Cooperative Growth Study (NCGS) sponsored by Genentech Inc.

Price D, et al. *Hormone Res* 1998;49:91-97.

**Editor's comment:** *These are important data and help answer the question: "When does one begin GH therapy in children with treated craniopharyngioma?" The individuals reported in this study began their treatment at a mean of 2.3 years after tumor diagnosis. What remains unclear is why the decision was made to begin therapy at that time.*

*The authors are correct in pointing out that their recurrence rate is greater than that from the NCGS in the United States for craniopharyngioma (6.4%). The conclusions from NCGS and the current report suggest that exogenous GH does not increase the risk for tumor recurrence.*

William L. Clarke, MD

*For a complete review of the diagnosis and management of craniopharyngioma, see GGH 1994;10(3):6-10.*

## Metabolic Effects of Long-Term Growth Hormone Treatment in Prepubertal Children With Chronic Renal Failure After Kidney Transplantation

Patients included in this report on metabolic data for the German Study Group for Growth Hormone Treatment in Chronic Renal Failure (CRF) had a height SDS of  $\leq -2.0$  and/or a height velocity  $< 25$ th percentile, a glomerular filtration rate (GFR) of  $< 60$  mL/min/1.73 m<sup>2</sup> in conservatively treated patients, and a GFR  $> 20$  mL/min/1.73 m<sup>2</sup> in patients after renal transplantations (RT). Fifty-three children were prepubertal at the start of recombinant human growth hormone (rhGH) therapy and remained prepubertal throughout the observation period. Twenty-nine of the patients were on conservative treatment for CRF, 14 patients were on dialysis, and 10 other patients had functioning renal allografts. All were on immunosuppressant therapy with cyclosporine, azathioprine, and methylpred-nisolone.

Twelve healthy prepubertal children being evaluated for idiopathic short stature formed the control group. None had rhGH deficiency but had received rhGH therapy. The CRF patients received rhGH at a dose of 28 to 30 IU/m<sup>2</sup>/d (0.31 to 0.33 mg/kg/d). Control subjects received rhGH 24 IU/m<sup>2</sup>/d (0.26 mg/kg/d). Biochemical examinations included Hb<sub>A1c</sub>, GFR, and a standard oral glucose tolerance test (OGTT), including insulin values.

Prior to administration of rhGH, Hb<sub>A1c</sub> and glucose responses during the OGTT were significantly elevated in all patient groups compared with controls. Fasting and integrated glucose concentrations were significantly higher in dialyzed patients than in those treated conservatively or those with RT. As anticipated in RT patients, the fasting 2-hour postprandial glucose was

positively correlated with the daily corticosteroid doses. Fasting serum insulin levels were elevated in the renal failure patients, with the highest levels being in the posttransplant group.

Fasting and OGTT glucose responses did not change throughout the observation period. However, fasting and stimulated insulin levels were 2-fold increased compared with baseline after the first year of rhGH therapy in the dialysis and RT patients, as well as in the controls. Insulin levels in the conservatively treated group became significantly elevated only after the second treatment year. Four patients, 2 on conservative treatment, 1 on dialysis, and 1 RT recipient, developed transient impairment of oral glucose tolerance as defined by the National Diabetes Group of the National Institutes of Health.

In conclusion, the authors observed a selective increase in fasting and glucose-stimulated insulin secretion without a change in glucose tolerance in patients with CRF after RT, but also in short normal children in response to rhGH therapy. This phenomenon was exaggerated in patients on dialysis and after RT, and persisted for up to 5 years of rhGH treatment. Although the absence of increased glucose intolerance during long-term rhGH treatment is

reassuring with respect to the diabetogenic potential of rhGH, the persisting hyperinsulinemia, combined with the dyslipidemia associated with CRF, raises concerns that rhGH therapy may contribute to the long-term risk for premature atherosclerosis in patients with childhood-onset CRF.

Haffner D, et al. *Pediatrics* 1998;43:209-215.

**Editor's comment:** *This interesting study demonstrates that the effects of rhGH on glucose-stimulated insulin secretion are not different for children with CRF and those with idiopathic short stature. The authors point out that associated hyperinsulinemia may be of particular concern in children with uremia and other factors, including dyslipidemia, which may contribute to atherosclerosis. These data are compatible with those reported on US patients and summarized in GGH (1996;12[4]:49-53) by Dr. Richard Fine. He points out in his review that there have been no clinical consequences associated with the hyperinsulinemia, as corroborated by the German Study Group. However, the long-term effect of such treatment remains to be shown.*

William L. Clarke, MD

## Familial Hyperinsulinism Caused by an Activating Glucokinase Mutation

Hyperinsulinism (HI) is relatively common. It is the most common cause of hypoglycemia. Affected individuals are at risk for seizures and permanent brain damage. Glaser et al describe a family with HI associated with a mutation in the glucokinase gene. Glucokinase is an enzyme with low affinity for glucose that controls the rate-limiting step of beta-cell glucose metabolism.

A mutation of the glucokinase gene has been detected in a 31-year-old white male, his 2 children, his sister, and his father. The mutation was sought in the proband after he became unconscious with low plasma glucose (38 mg/dL)

and elevated insulin levels. Counter regulatory hormone responses were normal, and so were pancreatic CT and MRI findings. The proband's 2 children had hypoglycemic seizures and also were diagnosed with HI. Urinary amino acids and urinary and plasma carnitines were normal, as was a pancreatic ultrasound. The proband's sister was diagnosed as having hypoglycemia at the age of 15 years; she had low fasting blood glucose and high plasma insulin levels, and later developed multiple sclerosis. Oral glucose tolerance tests in the proband and his sister showed hypoglycemia 3 hours after taking glucose. During hypoglycemia, their plasma insulin and C-peptide concentrations were elevated. In the proband and his sister, exogenous insulin administration resulted in a decrease in plasma glucose and plasma C-peptide concentrations. The proband's sister's children were normal. The proband's father had symptoms of hypoglycemia, which were controlled by diet. At the age of 48 years, the father developed insulin-dependent diabetes mellitus. All the affected family members were treated with diazoxide 100 to 300 mg/d. This same mutation was not detected in 37 unrelated white families, including 6 with an apparently autosomal dominant form of hyperinsulinism.

The *Val455Met* mutation in the glucokinase gene results in an increased affinity of glucokinase for glucose, resulting in a higher rate of glycolysis and therefore a higher rate of insulin secretion. This represents a

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