

age. One developed an intracerebral hemorrhage. An additional patient was microcephalic at birth. None of the 18 female offspring had malformation of the external genitalia. Follow-up of the 31 offspring, 6 of whom were less than 5 years of age, 7 of whom were between 5-10 years, and 18 who were older than 10 years of age at the time of evaluation, revealed that all were growing, maturing, and developing normally.

Krone N, et al. *Clin Endocrinol* 2001;55:523-529.

First Editor's Comment: *These data are encouraging in that women with simple virilizing and non-classical CAH are often able to conceive and deliver healthy children, thus confirming previous reports. More data on the degree of adrenal suppression during pregnancy, and knowing post-natal neonatal adrenal function would have been of interest.*

That only one of 48 women with salt-losing CAH had an infant illustrates the difficulties still encountered in the management of many of these patients. As Krone et al discuss, the relative infertility of women with CAH may be due to hormonal (hyperandrogenism), anatomic (inadequate reconstruction of the vagina), or psychosocial factors (behavioral masculinization, low marriage rate, and/or sexual preference). It is anticipated that prenatal detection and treatment of females with CAH and establishing neonatal screening programs for this disorder will change substantially the "natural history" of pregnancy in females with CAH.

Regarding surgical reconstruction of the external genitalia in the virilized female, while clitoroplasty may be appropriate in the neonatal period, vaginoplasty

should be deferred until the peri menarchal period, as earlier reconstructive surgery is usually inadequate.¹ In 39 adolescent phenotypic females (20 with CAH) (mean age at examination 15 years) who underwent vaginal surgery in infancy at a median age of 10 months, Creighton et al found that approximately 60% had a good or satisfactory cosmetic appearance of the external genitalia, but almost all required further surgery to permit use of tampons during menses and, presumably, sexual relations in adulthood.

Allen W. Root, MD

Second Editor's Comment: *Much is being discussed and written in 2002 regarding surgery on the genitalia of patients with enlarged clitorises. The current recommendation of many surgeons and pediatric endocrinologists is that surgery on the clitoris be delayed in most cases in the newborn period. For more details the reader is referred to references 1, 2, and 3 below. A lead article concerning the dilemmas of gender assignment and surgery will be published soon in GGH to provide up-to-date considerations for you our reader.*

Robert M. Blizzard, MD

References

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2. Creighton S and Minto C. *Brit Med J.* 2001;323:1264-1265.
3. Ramecroft L and Members of the Working Party of the British Association of Pediatric Surgeons on the Surgical Management of Ambiguous Genitalia. Available from: <http://www.baps.org.uk/documents/Intersex%20statement.htm>.

Growth Hormone Improves Clinical Status in Prepubertal Children with Cystic Fibrosis: Results of a Randomized Controlled Trial

Hardin and colleagues studied the effects of recombinant GH (0.3 mg/kg/wk) in 10 children with cystic fibrosis (CF) (ages 7-12, Tanner stage I) as compared to a control group of 9 similar children. All children recruited for the study were $\leq 10^{\text{th}}$ percentile for both height and weight and had adequate caloric intake as determined on 2 evaluations. Only one had an abnormal growth hormone stimulation test. Children were excluded from the study if they had been hospitalized within 6 weeks or had been treated with systemic or oral steroids within 6 weeks. Evaluations were made of pulmonary functions including forced vital capacity (FVC) and forced expiratory volume at 1 second (FEV₁). In addition, peak expiratory pressure (PEP) and peak inspiratory pressure (PIP) were measured. Resting energy expenditure, was determined using indirect calorimetry, and lean body mass was determined by

whole body dual energy x-ray absorptiometry. Studies were made at baseline and every 3 months. Data were collected with regard to the number of hospitalizations and antibiotic therapy. All data for both the treatment group and the control group were similar at baseline.

The height and weight Z scores were significantly greater in the treatment group after one year than in the control group; furthermore the treatment group had a significant increase in lean body mass. Additionally, at 12 months the treatment group had a significant improvement in percent FVC, PIP, and PEP. There was no significant change in percent FEV₁. The GH treated group had a significant decrease in the number of hospitalizations, although outpatient antibiotic therapy was not different between the two groups. There was no significant change in resting energy expenditure or nutritional intake during the study and carbohydrate

intolerance did not develop in either group. The advancement in bone age over the 12 months was not different between the two groups.

The authors conclude that growth hormone therapy is of significant benefit to pre-pubertal children with CF in terms of their height, weight, body composition, pulmonary function, and number of hospitalizations.

Hardin DS, et al. *J Pediatr* 2001;139:636-642.

First Editor's Comment: *This study by Hardin and associates is the first randomized, controlled trial of growth hormone therapy in children with cystic fibrosis. The findings are highly significant, although they have only been collected for a single year. Many questions remain unresolved. It would be important for studies to be undertaken to determine whether or not the change in lean body mass was due to an improved use of ingested calories and protein as suggested by the authors. In addition, the long-term benefits of treatment need to be evaluated, and the optimal dose needs to be determined. Furthermore, it will be important to follow these children to determine whether or not they are at increased risk for glucose intolerance over time. Hardin and associates have provided the preliminary data necessary to undertake a much larger scale study of the use of growth hormone in these children.*

William L. Clarke, MD

Second Editor's Comment: *Growth Hormone treatment in patients with cystic fibrosis has been shown*

to be of benefit in various short-term trials.^{1,2} However this is the first randomized controlled trial of GH treatment in patients with this disease. Growth hormone resulted in improved clinical status and increased growth. In CF, malnutrition develops as a result of unfavorable energy balance caused by a combination of poor intake, malabsorption of nutrients, chronic pulmonary disease and increased energy expenditures. Malnutrition adversely affects the course of the disease as well as the survival of the patients. Therefore any means to improve the anabolic state of CF patients may be of benefit. In this study GH treatment also improved the quality of life. Nonetheless, detrimental effects of GH treatment could occur in patients with CF, as diabetes is prevalent among this population.³ Although in this study no patient developed this problem, the data cannot be extended to other patients or to those who would undergo a longer-term treatment. It should also be kept in mind that improvements in growth and nutrition status of CF patients may be accomplished with aggressive nutritional supplementation without GH treatment.⁴

Fima Lifshitz, MD

References

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2. Hardin DS, et al. *Horm Metab Res* 1998;30:636-641.
3. Lang S, et al. *BMJ* 1995;311:655-659.
4. Dalzell J *Ped Gastroenterol Nutr* 1992;15:141-145.

Intake of Vitamin D and Risk of Type I Diabetes: A Birth-Cohort Study

To ascertain whether vitamin D supplementation or vitamin D deficiency in infancy could affect the development of type I diabetes, a birth-cohort study was done in Oulu and Lapland, Finland. All infants born in 1996 were studied (n = 12,055). Data were collected on vitamin D supplementation and on the presence of suspected rickets during the first year of life. The primary outcome measured was the diagnosis of type I diabetes by the end of 1997 (30 year follow-up). Of the 10,366 children included in the analysis, 81 were diagnosed with type I diabetes. Vitamin D supplementation was associated with a decreased frequency of this disease. Children who took the recommended 2000 IU of vitamin D on a daily basis had a rate ratio of 0.22 of developing the disease, as compared with those who received no vitamin D. The rate ratio in those who received a lesser amount of vitamin D supplementation was 0.12. Children suspected of having rickets during the first year of life had a rate ratio of 3.0 as compared with those without

such diagnosis. The authors concluded that vitamin D supplementation was associated with a reduced risk of type I diabetes.

Hypponen E, et al. *Lancet* 2001;358:1500-1503.

First Editor's Comments: *This is a very provocative study implicating the deficiency of one hormone (vitamin D) on the development of another hormone deficiency (insulin). The mechanisms of such association were thought to be related to the triggering of an immune process resulting from the lack of vitamin D. This is consistent with data from animal studies, and with the observation that cod liver oil supplementation during pregnancy is associated with a reduced rate of type I diabetes in the offspring.¹ The Eurodiab study also showed that vitamin D supplementation in early childhood may prevent this disease.² However, only 0.3% of infants in the Eurodiab study were not given*