Not All Growth Disorders Reflect Hormone Deficit

BY HEIDI SPLETE
Senior Writer

BALTIMORE — Consider a wide range of causes when evaluating a child for a growth disorder, Leslie Plotnick, M.D., said at a meeting on pediatric endocrinology sponsored by Johns Hopkins University.

Although growth hormone treatment is approved by the Food and Drug Administration for some conditions, not all children with growth problems are growth hormone deficient, and a thorough evaluation is important, including a complete history and physical examination.

"A child with normal growth will track along a percentile line," said Dr. Plotnick, a pediatric endocrinologist at Johns Hopkins University. Growth velocity normally decreases prior to puberty, until the adolescent growth spurt begins.

Consider evaluating children for growth problems when the growth rate is less than 5 cm/yr from age 3 years to 12 years, Dr. Plotnick advised. In addition, consider the possibility of a growth disorder when a child's height is below the 5th percentile or when height drops across percentiles over time. Another sign is when a child's height is more than two standard deviations below the average height of the biologic parents.

Causes of short stature or poor linear growth include major organ system diseases that are cardiac, pulmonary, renal, gastrointestinal, nutritional, hematologic, or CNS-related. In addition, chromosomal disorders such as Turner's syndrome; intrauterine growth retardation; endocrine disorders; or, simply, familial short stature or constitutional growth delay can cause a child to grow at a slower than average rate.

Although evidence of any association remains uncertain, oral or inhaled glucocorticoids might contribute to delayed growth. Long-term data on the impact of other medications—including stimulants, antidepressants, antiseizure medications, and antipsychotics—on growth delay remain inconclusive as well.

Carefully monitor height and weight patterns in children who take these medications, Dr. Plotnick said. Changes from established pretreatment growth patterns suggest a medication effect and may require further evaluation.

Endocrine-related causes of short stature include hypothyroidism, cortisol excess, pseudohypoparathyroidism, poorly controlled diabetes mellitus, and growth hormone deficiency. Features associated with these conditions include goiter, dry skin, midline defects, micropenis in boys, and an especially round, cherubic face.

The screening work-up for short stature is extensive and includes a complete metabolic profile, complete blood count, thyroid function test, and celiac screen.

A definitive diagnosis of growth hormone deficiency requires at least two tests that indicate a growth hormone level of less than 10 ng/mL, including arginine, L-dopa, clonidine, glucagon, and insulin-induced hypoglycemia. If a child appears to have growth hormone deficiency, conduct a brain MRI and test other pituitary axis hormones, she added.

Growth hormone deficiency can be congenital or genetic, or it can be acquired as a result of brain tumors, infiltrative diseases, head trauma, infection, central nervous system surgery, or central nervous system irradiation to treat a tumor.

For more specific information about growth patterns in children and to download the current growth charts from the Centers for Disease Control and Prevention, visit www.cdc.gov/growthcharts. ■

Dosing Growth Hormones to IGF-1 Levels More Effective

BY BETSY BATES
Los Angeles Bureau

SAN DIEGO — Short children grew far taller when their growth hormone doses were adjusted according to their insulin-like growth factor 1 levels rather than to their weight, according to randomized study results.

"IGF-1 levels do matter," said Pinchas Cohen, M.D., professor and director of research and training in the division of endocrinology at the University of California, Los Angeles, School of Medicine.

The notion of targeting dosing in order to maximize height in children of short stature is somewhat new and had been thought clinically impractical, Dr. Cohen said at a clinical symposium during the annual meeting of the Endocrine Society.

However, it was "possible and doable" to adjust doses according to a simple IGF-1–based algorithm. This approach resulted in "significant, quite dramatic improvement in height" for some children enrolled in the 2-year, multicenter trial.

In all, 172 children diagnosed with growth hormone deficiency or idiopathic short stature were enrolled in the trial sponsored by Novo Nordisk Inc., a manufacturer of human growth hormone, and the Lucile Packard Foundation for Children's Health.

The children were aged 3-15 years and significantly below normal height for their age, with a mean standard deviation score of –2.63. They also had low levels of IGF-1, the core mediator of growth hormone action on linear growth.

The complex study design featured a control group of 34 children who received a conventional 40 mcg/kg per day dose of growth hormone. Two other groups received targeted, adjustable doses of growth hormone based on IGF-1 levels at 3-month checkups.

One group received growth hormone in amounts necessary to achieve normal IGF-1 levels, and included 70 children. The other group, which numbered 68 children, received enough growth hormone to drive their IGF-1 levels two standard deviations above the norm.

The three groups achieved mean IGF-1 levels of +0.4, +0.4, and +2.0 standard deviation scores in the first 9 months of the study, and doses of 41 mcg/kg per day, 33 mcg/kg per day, and 110 mcg/kg per day were required to sustain these levels, said Dr. Cohen.

Only a small, nonsignificant difference was seen in children receiving standard growth hormone doses according to weight and those receiving doses targeted at a normal IGF-1.

The big difference in height was seen in children who received growth hormone at a dose aimed at raising their IGF-1 levels to two standard deviations greater than the norm. In this group, children with growth hormone deficiency grew 45% more, and children with idiopathic short stature grew 58% more than children in the other groups.

Side effects and adverse events were similar in all three groups.

Interestingly, a huge variability was seen in the amount of growth hormone required to maintain targeted IGF-1 levels among individual patients: 9-114 mcg/kg per day in the first targeted group and 20-346 mcg/kg per day in the second.

Dr. Cohen serves as a consultant or advisory board member or receives research support from a number of companies that manufacture human growth hormone, including Genentech Inc., Pfizer Inc., Eli Lilly & Co., Novo Nordisk Inc., and Serono Inc. ■

ICMA Gonadotropin Test Called The Best Lab Evidence of Puberty

BY DOUG BRUNK
San Diego Bureau

YOSEMITE, CALIF. — The best laboratory evidence of puberty is a test for luteinizing hormone and follicle-stimulating hormone done by immunochemiluminometric assay, Stephen M. Rosenthal, M.D., said at a pediatric conference sponsored by Symposia Medicus.

Two labs that run the tests are Esoterix Inc. and Quest Diagnostics Inc., said Dr. Rosenthal, professor of pediatrics at the University of California, San Francisco.

"If you ever order tests for LH and FSH, it's very important that you order them by immunochemiluminometric assay (ICMA), because [the tests] are able to distinguish between someone who's prepubertal and the different Tanner stages," he said.

If you get results that are difficult to interpret, Dr. Rosenthal recommended doing a GnRH stimulation test, which is also called a luteinizing hormone releasing factor (LRF) stimulation test. This involves giving a synthetic bolus of GnRH and then measuring the patient's levels of LH, FSH, and either estradiol or testosterone.

Dr. Rosenthal noted that there have been availability problems with GnRH. If GnRH is not available, a similar test can be done with leuprolide acetate, a GnRH agonist. Guidelines for carrying out the latter test are described in the following reference: J. Clin. Endocrinol. Metab. 1994;78:30-5.

"If you give an injection of synthetic GnRH [or agonist] to somebody who's in puberty, their own pituitary gland has been primed by their own GnRH; so when you give it, you're going to see a vigorous rise in LH," he explained.

The differential diagnosis of delayed puberty is defined clinically as a girl who has no evidence of breast development by age 13 years or a boy who has no evidence of testicular enlargement by age 14 years. The following are general possibilities in this differential diagnosis:

► **Constitutional delay in growth.** Most children seen for concerns about delayed puberty will fit this category.

"This is one of those interesting scenarios where it appears that people not only grow more slowly and reach puberty more slowly, it's like there's something in their biological clock that makes them age more slowly," Dr. Rosenthal noted. "They ultimately reach a normal adult height and full pubertal development; it just takes them longer to get there. This often runs in families. Is it possible that these kids actually age more slowly as they grow older, even as adults?" he asked. "Is there something to be learned here to give us some insight? We don't know the answer to that yet because there are so many variables as we get older that affect longevity."

Some 'people not only grow more slowly and reach puberty more slowly ... [they] age more slowly.'

DR. ROSENTHAL

► **Hypogonadotropic hypogonadism.** In this condition, the defect is located in the hypothalamus or in the pituitary gland. The cause could be Kallmann syndrome or could be associated with other conditions including cleft palate; congenital deafness; the X-linked form of congenital adrenal hypoplasia; Prader-Willi syndrome; Laurence-Moon-Biedl syndrome; central nervous system disease; and a variety of other conditions such as hypothyroidism, poorly controlled diabetes, and anorexia nervosa.

► **Hypergonadotropic hypogonadism.** In this condition, the defect is in the testes or ovaries. Potential causes include Klinefelter's syndrome and its variants; anorchia; cryptorchidism; XY gonadal dysgenesis; Noonan's syndrome; Turner's syndrome and its variants; and XX gonadal dysgenesis. ■