Editorial

Effects of Growth Hormone in Prader-Willi Syndrome

Ellen L. Connor, M.D.
Arlan Rosenbloom, M.D.

Prader-Willi syndrome (PWS) is a genetic condition characterized by infantile failure to thrive and hypotonia, followed in childhood by impressive hyperphagia and morbid obesity. Associated features are almond-shaped eyes, typical simplified facies, small hands and feet, hypogonadism, moderate short stature, and mental retardation with an IQ range of 20 to 80.[1] Most patients (75%) have an identified paternal deletion of the chromosome 15q region. Among the remaining patients, 60% can be found to have uniparental disomy, in which two maternal copies of the 15q region are present.[2]

Described in this issue of *Clinical Pediatrics* is the use of recombinant human growth hormone (GH) in a patient who has some of the clinical features of PWS, but neither the genotype nor history of hyperphagia and morbid obesity.[3] At the time of provocative growth hormone testing (age 2.5 years), the child had a weight-for-height measurement at the 50th percentile and growth hormone levels consistent with a diagnosis of growth hormone deficiency. The somatomedin-C concentration, however, was normal, indicating functional growth hormone sufficiency. What is unique about this particular case report is the finding that the child experienced a reduction in weight-for-height during five years of GH therapy, reportedly without parental restriction of his caloric intake. The validity of the dietary history is questionable since there was little growth response to GH therapy; thus, either the child was not GH-deficient and, therefore, not responsive to GH or his caloric intake was being severely restricted, impairing his ability to respond.

Division of Pediatric Endocrinology
University of Florida
Gainesville, Florida

Address correspondence to: Ellen L. Connor, M.D., Pediatric Endocrinology, University of Florida, P.O. Box 100296, Gainesville, FL 32610

After five years of GH therapy, the child's weight was at the 10th percentile for height, a reduction from the 75th to 90th percentile at the initiation of therapy. A slight increase in height percentile from less than the fifth percentile to the fifth percentile was observed over five years of GH administration. Growth hormone has been previously administered to five children with PWS with equally unimpressive results.[4,5] This latest report raises the issue of whether recombinant human growth hormone therapy is indicated in the management of the morbidly obese child with PWS.

Hypothalamic or pituitary dysfunction resulting in growth hormone deficiency in children with PWS has previously been proposed. Interpretation of the diagnostic GH levels is complicated by the patients' obesity. Obesity lowers GH responses to stimuli. Of six patients with PWS studied by Costeff et al[6] with 12-hour GH secretion studies and clonidine GH stimulation testing, all had weight-for-height measurements greater than 105% (range 107% to 186%). Furthermore, three of these six children had at least one peak GH level greater than 7 ng/dL, despite the confounding effect of obesity.

The notion that the lipolytic effect of GH and its ability to increase lean body mass are responsible for the decreased weight-for-height in the patient of Ruvalcaba et al is attractive.[7] This effect, however, cannot be explained by a moderation of appetite, since patients with documented GH deficiency typically have remarkable increases in appetite in the first six months of GH therapy. It is common for some children with documented GH deficiency, particularly those with organic lesions, to remain or become obese despite years of growth hormone administration. As noted above, the history, the diagnosis of GH deficiency, and the response to therapy are discordant in this patient report.

There will be increasing pressure to use recombinant GH therapy for children with PWS, Down syndrome,[8] or other syndromic causes of short stature for improvement in body composition and final height. Studies of GH therapy in girls with Turners syndrome have documented an increase in final height (151.9 cm treated, compared with 143.6 cm untreated).[9] Is there a benefit in making a small person slightly taller at $15,000 to $25,000 per year? We must weigh these considerations on an individual basis. Growth curves are based upon the normal distribution of a given population; pathology is not inherent to a specific level of deviation. A functional definition might be more appropriate. Thus, if a young woman with PWS would be mentally able to work at a checkout counter and GH therapy would allow her to reach across the counter, the therapy, if proven effective, would indeed warrant consideration.

Pharmacologic doses of growth hormone may be effective in increasing linear growth velocity in children with PWS and also may be found to have some effect in improving lean body mass in these children. If such therapy is the case, it will be necessary to weigh known benefits against potential risks of GH therapy. Such therapy has been associated with a number of side effects that might be more likely to occur in children with PWS. These include pitting edema secondary to sodium retention, worsening scoliosis, slipped capital femoral epiphyses, the development of glucose intolerance, and the unmasking of hypothyroidism.

A trial of GH therapy should be undertaken only when both the physicians and family members have openly examined their expectations.[10] Children should be included in these discussions as appropriate for their level of intellectual functioning. Previous experience with other children with short stature not due to GH deficiency has demonstrated that, although growth velocities may be increased in the first one to two years of therapy, growth hormone administration may have no effect on final height.[11] Parents and children must be prepared for this possible outcome, and physicians must be sensitive to the possibility that the family's disappointment may lead to disappointment in the child who does not become slimmer or grow. Similarly, the child's disappointment at not achieving an imagined body image should also be anticipated and addressed even before GH therapy is attempted. More difficult to identify will be the family's unconscious hope that taller stature will make a child with a genetic syndrome more normal.

The use of recombinant growth hormone in the child with obesity and short stature in the context of PWS or the use of growth hormone in any child with syndromic short stature should be initiated with caution and realistic expectations. A team approach that draws upon the expertise of the endocrinologist, geneticist, psychologist, and dietitian will provide optimal care and evaluation of these children and should allow the acceptance of reasonable goals of therapy. In the words of Ralph Waldo Emerson, "No virtue goes with size." There is virtue in preventing or reducing the morbid obesity of the child with PWS, but the case for growth hormone's doing so has yet to be made.

REFERENCES

1. Jones KL. In: Smith DA, ed. *Smith's Recognizable Patterns of Human Malformation.* 4th ed. Philadelphia, PA: WB Saunders Co; 1982:170-171.
2. Mascari MJ, Gottlieb W, Rogan PK, et al. The frequency of uniparental disomy in Prader-Willi syndrome. *N Engl J Med.* 1992;326:1599-1607.
3. Ruvalcaba RHA, Holm VA. Effects of growth hormone in Prader-Willi syndrome: a case report. *Clin Pediatr.* 1993;32:292-295.
4. Lee PDK, Wilson DM, Hintz RL, Rosenfeld RG. Growth hormone treatment of short stature in Prader-Willi syndrome. *Am J Med Genet.* 1987;28:865-871.
5. Raiti S, Trias E, Levitsky L, Grossman MS. Oxandrolone and growth hormone: comparison of growth-stimulating effects in short children. *Am J Dis Child.* 1973;126:597-600.
6. Costeff H, Holm VA, Ruvalcaba R, Shaver J. Growth hormone secretion in Prader-Willi syndrome. *Acta Paediatr Scand.* 1990;79:1059-1062.
7. Walker JM, Bond SA, Voss LD, et al. Treatment of short normal children with growth hormone — a cautionary tale? *Lancet.* 1990;336:1331-1334.
8. Torrado C, Bastian W, Wisniewski KE, Castells S. Treatment of children with Down syndrome and growth retardation with recombinant human growth hormone. *J Pediatr.* 1991;119(3):478-483.
9. Rosenfeld RG. Nonconventional growth hormone therapy in Turner syndrome: the United States experience. *Horm Res.* 1990;33:137-143.
10. Underwood LE, Van Wyk JJ. In: Wilson JD, Foster DW, eds. *Williams Textbook of Endocrinology.* 8th ed. Philadelphia, PA: WB Saunders Co; 1992;21:1123-1124.
11. Albertsson-Wikland K, Karlberg J. Effect of GH treatment in short children on the timing of puberty and final height. *Horm Res.* 1991;35(suppl 2):32.